British Journal of Diseases of the Chest

EDITORS
J. R. BELCHER and J. SMART

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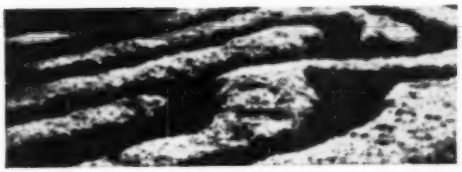

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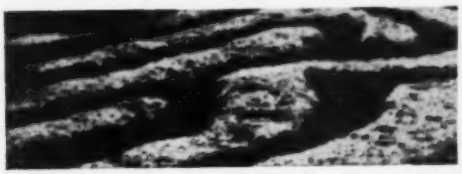

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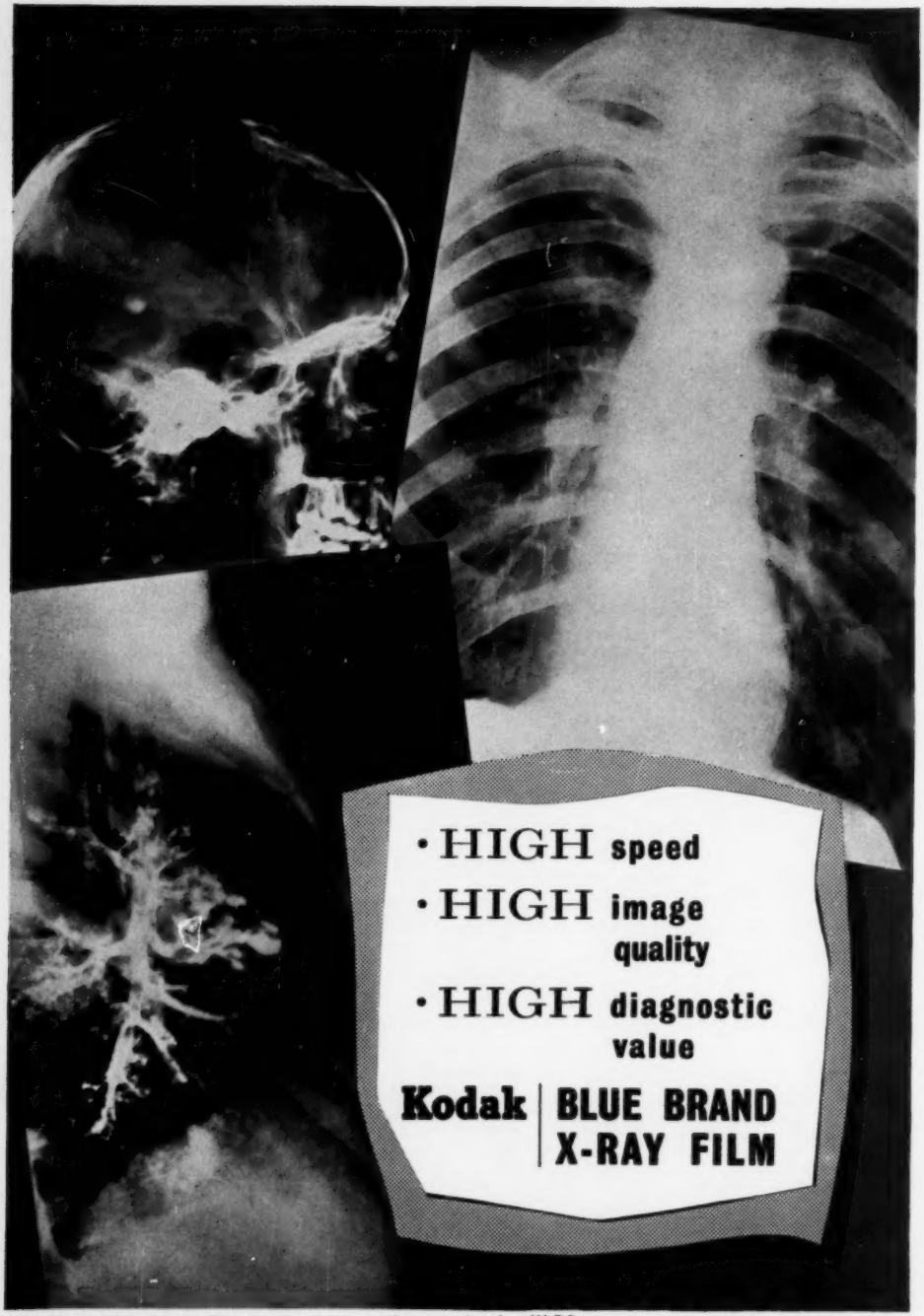

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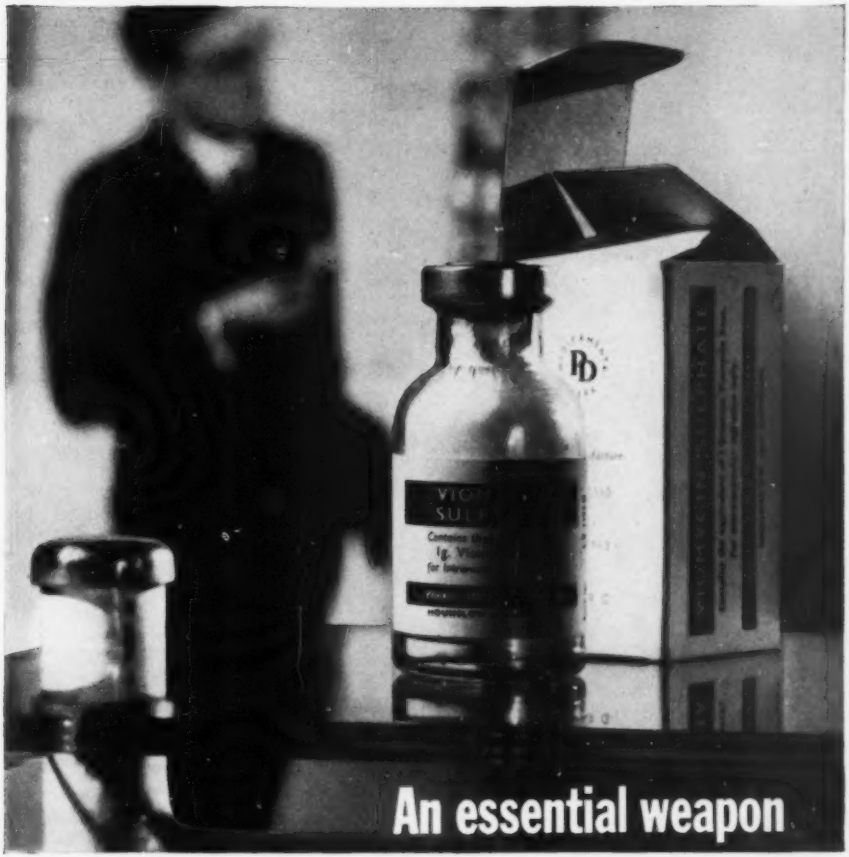

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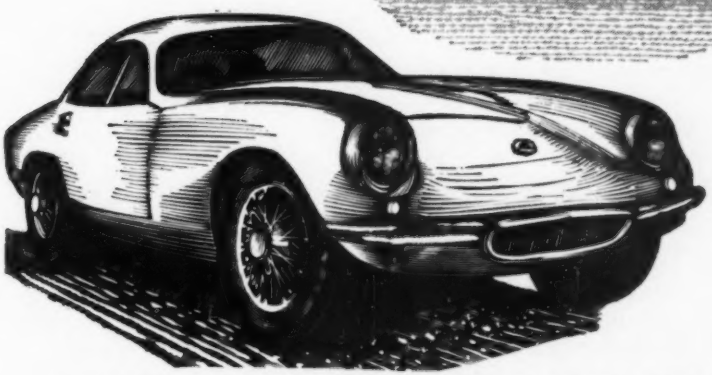

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Brit. J. Dis. Chest (1961) **55**, 49.

A SAMPLING METHOD FOR ESTIMATING THE NUMBER OF MUCOUS GLANDS IN THE FŒTAL HUMAN TRACHEA

By W. M. Thurlbeck,* B. Benjamin and Lynne Reid

From the Institute of Diseases of the Chest, Brompton Hospital, London, S.W.3

Since excessive secretion of mucus is the dominant feature of chronic bronchitis and bears close relationship to the concentration of mucus-secreting structures in the whole respiratory tract, this study was undertaken to determine the concentration and distribution of the mucus gland ducts in the trachea—a convenient unit in which to study their development and morphology. The purpose of this paper is to describe a detailed study of a small series of tracheas designed to establish a method by which, from a small number of sections, the total number of mucous glands in the trachea can be estimated. A further communication on page 54 describes the gland variation found between different fœtuses.

Material and Methods

The trachea was taken as beginning midway between the cricoid cartilage and first tracheal ring and as ending at the carina; in both cases the plane taken lay at right angles to the long axis of the trachea.

The tracheas of 10 fœtuses between 9½ and 28½ weeks of gestation were serially sectioned and the total number of sections was recorded. In 5 specimens every section was stained; in the remaining 5 between 30 per cent. and 65 per cent. were selected and stained in groups of from 60 to 340 consecutive sections. In 4 specimens sections were in the longitudinal plane, in 6 in the transverse. Because the trachea widens at its caudal end, transverse serial sections of this part were studied in 4 fœtuses. In all about 6,500 sections were studied.

A micrometer scale was placed over the sections to subdivide them for purposes of counting and to make it possible to orientate a section in relation to its neighbours. The results were recorded on graph paper, the position of the ducts in relation to the micrometer scale being noted, together with the number of slides in which the opening of the duct of the epithelial surface was visible. The frequency with which any level of the trachea was examined was ascertained by considering each trachea as consisting of 100 units. Thus it was possible to compare the same level or position, relative to the entire length of the trachea.

Results

It was soon apparent that transverse sections were more suitable for counting ducts than longitudinal ones, for the work entailed in examining

* Present address: Dept. of Pathology, Massachusetts General Hospital, Boston 14, Mass., U.S.A.

(*Received for publication February* 2, 1961.)

tangential sections was time-consuming and it was difficult to record the duct openings. Further, the greater length of trachea on longitudinal sections made it hard to superimpose the micrometer scale.

The distribution of sampling at 100 regular intervals through all the tracheas showed that an average of six tracheas were represented at each level and that rarely was this less than five or more than seven, only 10 per cent. of levels being outside this range. Although in some tracheas not every section was examined, the groups of sections examined were widely and randomly distributed and, consequently, calculations could be made of the distribution of ducts in the whole group of tracheas.

Examination of the material showed that in fœtuses of intra-uterine age up

TABLE I.—FINDINGS IN A TYPICAL TRACHEA

Block	*Number of sections*	*Mean number of ducts per section (with standard error of mean)*	*Mean number of sections over which ducts extended (and standard error of mean)*	*Estimate of number of ducts in block*	*Coefficient of variation per cent.*
A	60	8·28 ±0·40	4·34 ±0·16	114	5
B	60	8·37 ±0·31	4·15 ±0·20	121	5
C	60	8·90 ±0·37	4·66 ±0·21	115	5
D	60	8·43 ±0·36	4·61 ±0·15	110	5
E	60	8·25 ±0·37	4·70 ±0·17	105	5
F	60	9·77 ±0·42	4·93 ±0·15	119	5
G	60	9·48 ±0·34	5·01 ±0·16	114	5
H	60	8·67 ±0·28	4·37 ±0·14	119	5
I	60	9·18 ±0·20	4·35 ±0·14	127	4

NOTE. (1) $114 = [60 \times 8{\cdot}28] \div 4{\cdot}34$.

(2) Mean No. of ducts per block based on A − H = 115.

(3) $115 \times 1{\cdot}125$ (factor for increase in diameter) = 129 which is number expected in block I; actual number was 127.

(4) Total sections in whole length of trachea = 1850.

(5) Estimate of total ducts is $115 \times \frac{1850}{60} \times 1{\cdot}011 = 3590$.

(6) The pooled estimate of the coefficient of variation of ducts per block of 60 sections obtained in two ways:

(i) From the distribution of Col. 5. This gives 4·6 per cent.

(ii) As in the case of the individual values in Col. 6, from the standard errors of the means in Cols. 4 and 5. These means are not independent since the longer the ducts persist in serial sections the higher the total present per section (the coefficient of correlation is 0·58). This gives 3·7 per cent.

So that 4 per cent. seems to be a reasonable value to accept.

It will be seen that an estimate of the number of ducts based upon 60 consecutive sections will be subject to a coefficient of variation of about 4 per cent. Twice this margin on either side of the estimate is taken to include the true value on most occasions. "Most" here means 95 per cent. of estimates, so that in statistical language we speak of a 95 per cent. confidence interval. From 60 sections, then, we can estimate the total ducts within a margin of ±8 per cent. A more acceptable margin would be ±5 per cent. and this could be achieved if the coefficient of variation were reduced to 2½ per cent. as compared with 4 per cent. for 60 sections. An increase in the number of sections to 150 would reduce the coefficient of variation in the proportion of $\sqrt{60/150}$ or 0·6 and would be sufficient.

to 16 weeks the ducts were not distributed evenly, there being more ducts per unit length cranially than caudally. In fœtuses over this age the distribution was more even and this was especially true of the upper nine-tenths of the trachea; consequently only older fœtuses were used.

The lateral bulge in the middle of the trachea is so slight that it can be ignored, but the trachea broadens considerably at the confluence of the two main bronchi and, as measured in 6 fœtuses, the bulge involves about 8½ per cent. of the total length (Table I), being at its maximum between 20 per cent. and 25 per cent. of the average diameter. Roughly proportional to this broadening was a slight but significant increase in ducts per unit length (Tables I and II), the increase in the number of ducts being 12½ per cent. for this 8½ per cent. of length. This is equivalent to an overall increase of 1·1 per cent. on the number of ducts estimated for the whole trachea from levels above the broadening.

Tables I and II show an analysis of the data. Table I presents the findings in one specimen which was examined in great detail. Nine blocks, each of 60 consecutive sections, were taken, spaced fairly regularly along the length of the trachea and with the most distal block at the carina. Statistical analysis showed that the margin of error here was ± 8 per cent. but that if 150 sections were used the margin would be ± 5 per cent., a more acceptable one. The examination of such a sample is relatively easy as it takes only two hours or so and can therefore be used for comparing larger numbers. In addition it was necessary to section the whole of the trachea to estimate the fraction of the total number of sections represented by the 150 examined, so that from the number of ducts present in the block of 150 serial sections from the middle region of the trachea, together with the total number of sections, the number of ducts in the whole trachea could be estimated. To ascertain the number of ducts in the whole of the trachea, it is necessary to apply the corrective 1·1 per cent. indicated above to the figure thus estimated from the proximal part of the trachea.

In Table II, specimen BX 787 is compared with others and the results are generally consistent. Judging from the number of sections in which a particular duct can be recognised, the mean size of the duct varies from trachea to trachea, doubtless due in some part to variation in the plane of section and shrinkage. The considerable variation in the total number of ducts from fœtus to fœtus will be dealt with in a second paper.

Summary

From examination of mucous gland duct distribution in 10 fœtal tracheas it has been found that it is uniform in the proximal eleven-twelfths of the trachea after the sixteenth fœtal week. In the distal twelfth there are more ducts per unit length, which may be ascribed to the widening of the trachea near the carina.

To estimate the total number of mucous gland ducts in the trachea to within ± 5 per cent. it is necessary to discover the total number of ducts in a sample of 150 consecutive transverse serial sections (7μ used here), selected to

TABLE II.—VARIATION BETWEEN SPECIMENS

Specimen and total sections	*Block and number of sections*	*Mean ducts per section (and s.e. of mean)*	*Mean number of sections of which ducts extend (and s.e. of mean)*	*Number of ducts*	*Estimate of total from block (and co-efficient of variation scaled to one block of 60 sections)*	*Increase in radius (per cent.)*	*Per cent. increase of ducts in end block as compared with mean of other blocks*
BX754/2500	A 115	11·2 (0·295)	5·94 (0·163)	217	4,765 (0·027)		
	B 120	10·1 (0·254)	5·38 (0·152)	225	4,745 (0·027)		
	C 116			208	4,530 (0·027)		
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BX775/2000	A 120	9·17 (0·182)	6·55 (0·135)	168	2,830 (0·020)		
	B 120	10·5 (0·234)	6·83 (0·207)	185	3,115 (0·026)		
	C 120			164	2,765 (0·024)		
	D 120			163	2,745 (0·024)		
	E 116			166	2,795 (0·024)		
	A-D				2,830 (0·033)		
BX769/1550	A 120	9·01 (0·292)	5·05*	214	2,795 (0·033)		
	B 120	7·82 (0·220)	4·83*	194	2,535 (0·033)		
	C 120	7·18 (0·305)	4·01*	215	2,810 (0·033)		
	near end D 120	7·96 (0·237)	3·96*	241		11·5	16·0
	A-C				2,710 (0·046)		
BX788/2100	A 120			224	3,960 (0·030)		
	B 120			197	3,485 (0·030)		
	C 120			226	4,000 (0·030)		
	end:						
	D 60			119		10·9	10·3
	E 60			130		15·2	12·1
	F 40			91		20·0	26·6
	A-C				3,820 (0·043)		

* Apparent by reference to cols. 3 and 5.

avoid the region of the carina, and the number of sections at the same thickness (7μ) when the whole trachea is sectioned. A correction factor of 1·1 per cent. must be applied to the total number of ducts thus obtained to compensate for the increased number in the distal part.

An analysis of a large number of sections from a relatively small number of tracheas has yielded a formula by which the total number of glands in any trachea can be estimated, within a narrow margin of accuracy, from the examination of a relatively small number of sections.

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DEVELOPMENT AND DISTRIBUTION OF MUCOUS GLANDS IN THE FŒTAL HUMAN TRACHEA

By W. M. Thurlbeck, B. Benjamin and Lynne Reid

From the Institute of Diseases of the Chest and Brompton Hospital, London, S.W.3

The enquiry described in the previous paper (Thurlbeck, Benjamin and Reid, 1961) produced a suitable method of estimating the number of mucous glands in the trachea; it has been followed by a study of further tracheas, reported in this paper, with a view to gaining some idea of individual variation and of variation between male and female.

Material and Method

Of the 39 fœtuses (including the 10 used to establish the method), 23 were male and 16 female and, as estimated from the crown-rump length, of ages between 9 and 40 weeks. The first day of the mother's last menstrual period, when known, was recorded, the fœtus was weighed, the crown-rump and crown-heel measurements were taken and the sex was noted. The trachea, lungs and heart were then removed and the length, coronal and sagittal diameters of the trachea were measured—the last two at two levels.

Eight tracheas were serially sectioned longitudinally and 31 transversely. All sections from the longitudinally sectioned tracheas were stained. Of the transversely sectioned tracheas, all sections of one were stained; of 8 of the remaining 30, between 30 per cent. and 65 per cent.; and of the last 22, samples of 150 to 300 consecutive sections, taken from the middle third of the trachea—one section in ten being stained with Periodic Acid Schiff (P.A.S.), one in ten with Weigert's elastic tissue stain and counterstained with van Gieson, and the remainder with hæmatoxylin-eosin.

As it became difficult in fœtuses of more than 25 weeks to distinguish groups of acini as glands separate from their neighbours, ducts rather than glands were counted. Occasionally two well-defined, separate glands would open into the same duct, but since this probably represents a slight anatomical variant of embryological development from a single duct, they were counted as one.

Seventeen serially sectioned blocks were examined to assess the topographical relation of duct opening to cartilage and a " map " of the tracheal cartilage was superimposed on the chart of the duct openings (for the method see Thurlbeck, Benjamin and Reid, 1961). The number of these per unit area in regions of high cartilage was then compared with the number in areas of low cartilage from the same trachea. Reid's method (1960) of measuring the ratio of gland thickness to that of the bronchial wall was applied in 25 fœtuses. The depth of gland at a point overlying cartilage was measured and, at the same place, the distance of the epithelium from the inner layer of perichondrium; these were expressed as a ratio.

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Development of the Trachea

Mucous Glands

At 12 weeks the first sign of development of mucous glands was seen in the multiplication of the basal cells of the epithelium, which appeared as small protrusions or buds. They were present throughout the length of the trachea, though more numerous cranially than caudally. As the cells multiplied they bulged downward to form a solid cylindrical structure, which then developed a small central lumen visible at 13 weeks. At this age a few ducts had divided at their free end, with further divisions by 15 weeks, a process which had become well established at 16 and 17 weeks. Until this age ducts were more frequent and better advanced cranially than caudally, but afterwards the distinction was lost. At 16 weeks PAS positive material was found secreted in the duct epithelium.

Acini, recognisable as such and secreting mucus, began to appear at 18 weeks and became progressively better developed until, at 25 weeks, fully developed tubular-acinar glands were recognised. From this date until 40 weeks a progressively increasing proportion of glands seemed fully developed and in the thirty-seventh and fortieth week fœtuses all glands appeared to be fully developed. The gland/bronchial wall ratio pointed to a progressive increase in the relative amount of gland until the age of 25 weeks, after which time the mean gland-wall ratio remained in the region of 0·26 (standard error of mean, 0·012) the range of the ratio in the normal adult.

Goblet Cells, Cilia and Cartilage

In a 12-week fœtus intracellular vacuoles in the surface epithelium were recognisable, and at 13½ weeks well-defined goblet cells containing PAS positive material. Goblet cells had increased in number and by 16 weeks they were well developed and frequent. Cilia were first noticed at 13½ weeks and by 15 weeks they were well developed. Cartilage was present in the trachea of the youngest fœtus (9 weeks) some 3 weeks at least before the appearance of the first ducts. Comparison of the number of ducts per unit area of epithelium overlying cartilage, to the number of ducts per unit area of epithelium overlying interspace, showed no significant difference. The gland acini, however, were more prominent between the cartilage rings.

These details of the first appearance of certain structures in the wall of the trachea emerged during the examination of the groups of serial sections from which the total number of mucous ducts in the trachea were estimated. The gland totals found are here analysed statistically, according to the sex and age of the fœtus.

Sex and Individual Variability in Number of Mucous Glands in the Trachea

The data were first examined to determine the nature of any sex differences, age for age, in the number of glands; this disclosed male superiority. Since, age for age, the tracheal size tended to equality, the greater number of glands in

the male results from a higher concentration of glands rather than from a difference in the absolute size of the trachea. The data available indicates that there is a wide individual gland number variation at maturity, possibly from 4,000-6,000 for males and from 3,500-5,200 for females. The details of the analysis on which these results are based are given in the Appendix.

Discussion

The glands are usually pictured as developing between the eighth and tenth weeks from the bottom of crypt-like invaginations of the tracheal epithelium which appear progressively nearer to the periphery. In our material, duct formation began to show at the twelfth fœtal week, the ducts developing, as described by Bucher and Reid (1961), from the basal layer as a bud or solid protrusion in which only later a crypt-like space appears. Even at the earliest stage ducts were found at the distal portion of the trachea, although a greater concentration persists until the sixteenth or seventeenth week in the superior trachea, suggesting that cranially the development of ducts and glands is more advanced. Since the concentration of ducts remains constant until the thirtieth week at least, though the trachea steadily lengthens, new ducts must be forming throughout this period. Thereafter the rate of growth is so slow that in spite of the large number of fœtuses examined it was not possible to decide whether it continues at all.

As the glands grow, the ratio of gland thickness to wall thickness (Reid, 1960) reaches the adult norm in late fœtal life and this ratio is not exceeded. If such a ratio holds throughout childhood also, it offers an easy means of measuring gland hypertrophy at all ages.

The mean number of glands in the trachea is about 4,750 within a range of 3,500 to 6,000. No comparable figures are available for the adult lung, but the concentration of glands in the adult has been given as roughly one per square millimetre (von Hayek). Taking a trachea of diameter 2 cm. and length 10 cm., the estimated surface area would be 6,000 sq. mm., which, on the basis of one gland per square millimetre, means 6,000 glands. This is in the region of our counts and it may be that no very considerable increase in number occurs between birth and adult life.

How this is related to the number of glands in the whole of the lungs is uncertain, but from a study of the intrasegmental development of the mucous glands Bucher and Reid (1961) give as a rough preliminary estimate that the tracheal glands are about one-sixth of those in the lungs and trachea taken together—a substantial proportion considering the total length of bronchial pathways in the lung.

Any attempt to relate gland numbers to gland condition in chronic bronchitis necessarily calls at present for certain assumptions, of which the basic ones are: that the volume of glandular tissue is directly proportional to the number of ducts; that the volume of gland secretion varies directly with the total volume of glands; that the individual's gland endowment determines his response when irritation gives rise to hypertrophy—which means that the critical level of secretion which gives rise to sputum production is reached more quickly the

larger the number of glands. How far these assumptions are valid will only appear with time.

Hypersecretion by mucous glands resulting in sputum would seem to be a basic disturbance in chronic bronchitis and associated with measurable hypertrophy of the mucous secreting structures (Reid, 1960). Men are strikingly more prone to chronic bronchitis than are women and in men the disease is the more disabling. To discover whether a sex difference in the number of glands might contribute to the different incidence of chronic bronchitis between the sexes this study was undertaken; but the results do not give a clear-cut answer. They suggest that the number of glands in the female trachea is, after standardisation for age and length of trachea, less than in the male, and they also suggest that this difference derives from a lower concentration of glands in the female and is not just a reflection of the comparative shortness of the female trachea. In fact, the length of the male and female tracheas tend, age for age, to equality. But, although the impression is clear, individual variation is so great that our finding of male superiority in numbers of glands is statistically barely significant.

Apart from any sex variation these counts have emphasised the wide individual variation in gland number in the trachea. It might be expected that other bronchi would show a similar variation, although, because of differences between individuals in the pattern of branching of bronchi, comparison of gland number in bronchi is less satisfactory than in the case of the trachea. As the upper limit of the range in the trachea is almost twice that of the lower, the different response of individuals to the same environment may be due to their individual endowment with glands, and the lower concentration of mucous glands in the female may well be one factor accounting for her lower susceptibility to chronic bronchitis. This quantitative emphasis would seem to be justified in relation to a disease in which the abnormality—sputum production or hypersecretion of mucus—is an exaggeration of a normal function: in other words, primarily a quantitative disturbance.

Summary

1. In 39 fœtuses (23 male 16 female) the development of the mucous glands in the trachea has been traced and the number of mucous gland ducts counted by a method previously described.

2. Mucous gland buds can first be recognised at 12 weeks; they are more numerous cranially than caudally until the sixteenth or seventeenth week when such distinction is lost. Intracellular vacuoles can be recognised at 12 weeks, well-defined goblet cells and cilia at 13 weeks and secreting acini at 18 weeks. The cartilage, being seen at 9 weeks, is apparent approximately 3 weeks before the ducts.

3. Gland thickness expressed as a ratio to wall thickness reaches adult levels by 25 weeks. By 28 weeks seven-eights of the potential number of glands have appeared.

4. A lower total count was obtained for females than males, which arose from difference in concentration of the glands and does not reflect difference in the

size of the female trachea. Age for age the tracheal lengths for male and female tend to equality. Individual variation, however, is so great that it renders the sex difference only just significant statistically.

5. The data suggest that the asymptotic values for the maximum number of glands present at birth are 6,000 for males, 5,200 for females. A wide range of individual values is likely to occur, perhaps 4,000-6,000 for males, 3,500-5,200 for females.

6. The proportion of the total glands for the lung represented by those in the trachea is considered, and the possible clinical significance of gland number discussed.

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APPENDIX

Sex Differences in Number of Glands

The data were first examined to determine the nature of any sex differences, age for age, in the number of glands. The distribution of male specimens is shown in Table I.

Table I.—Male Specimens (23)

Age (weeks)	*Length of trachea (mm.)*	*No. of glands*		*A/E length of trachea*	*Adjusted expected glands*	*Residual difference from actual*
		Observed	*Fitted curve*			
9·0	—	0	290	—	—	—
10·0	4·0	0	370	0·847	310	−310
12·7	8·0	194	700	1·055	740	−550
13·2	7·5	1,150	790	0·926	730	+420
13·9	8·0	1,250	920	0·905	830	+420
16·0	11·0	1,600	1,440	0·994	1,430	+170
17·0	15·0	2,400	1,750	1·238	2,170	+230
18·1	15·0	3,350	2,130	1·129	2,400	+950
19·4	14·0	3,600	2,620	0·955	2,500	+1,100
20·7	14·0	2,700	3,130	0·873	3,730	−30
21·0	17·0	2,650	3,250	1·040	3,380	−730
22·3	17·0	3,900	3,750	0·959	3,600	+300
22·3	15·5	2,700	3,750	0·874	3,280	−580
22·5	17·0	3,500	3,820	0·948	3,620	−120
23·5	17·0	2,950	4,170	0·895	3,730	−780
23·5	21·0	5,200	4,170	1·105	4,610	+590
24·9	21·5	5,500	4,610	1·050	4,840	+660
25·6	23·0	5,500	4,800	1·084	5,200	+300
27·2	22·0	4,700	5,150	0·960	4,940	−240
29·5	25·0	5,300	5,500	0·987	5,430	−130
29·8	29·0	4,150	5,540	1·130	6,000	−1,850
37·0	34·0	5,600	5,930	1·022	6,000	−400
37·2	31·0	3,450	5,930	0·926	5,490	−2,040

The ages shown here are the mean of four estimates derived from the following criteria:

(i) Last maternal menstrual period.
(ii) Crown/rump length.
(iii) Fœtal weight.
(iv) Length of trachea (smooth curve fitted to data of column 2 of Table I).

On inspection it appeared probable that a typical logistic growth curve could be fitted to the numbers of glands shown in column 3 of the table. The figures themselves are shown as points indicated by crosses in Fig. 1 and the curve is shown as a continuous line. This, with an arbitrarily chosen limit of 6,000 glands, has the equation:

$$y = 6{,}000\ [1+215{\cdot}6e^{-0{\cdot}2630x}]^{-1}$$

where y = No. of glands and x = age in weeks. The calculated values from the curve are shown in column 4 of Table I. Having regard to the high variability of the material this fit is acceptable. The accumulated deviations amount to −3,170 and the estimate of the standard deviation of number of glands, after allowing for regression on age, is 920 or 17 per cent. of the expected value at age 30 weeks. This is more than three times the sampling error in counting the number of glands.

A similar curve having the equation

$$y = 5{,}200\ [1+196{\cdot}7e^{-0{\cdot}2508x}]^{-1}$$

was fitted to the female data shown in Table II.

The sigmoid curve for the female specimens is represented in Fig. 1 by a broken line, while the actual observations are represented by round dots. Here the accumulated deviations amount to +310 and the estimate of standard deviation is 870. The suggestion is that the development curves differ only in so far as the females appear to have a lower asymptotic value. Inspection of

TABLE II.—FEMALE SPECIMENS (16)

Age (weeks)	*Length of trachea (mm.)*	*No. of glands*		*A/E length of trachea*	*Adjusted expected glands*	*Residual difference from actual*
		Observed	*Fitted curve*			
12·8	7·5	330	600	1·016	610	−280
15·0	9·5	1,530	960	0·975	940	+590
18·8	13·0	2,400	1,930	0·941	1,820	+580
19·8	15·0	3,700	2,240	1·007	2,260	+1,440
20·3	16·0	3,350	2,410	1·037	2,500	+850
23·3	19·0	3,350	3,370	1·018	3,430	−80
23·3	18·0	4,650	3,370	0·965	3,250	+1,400
24·5	22·0	4,250	3,710	1·103	4,090	+160
24·5	22·0	4,100	3,710	1·103	4,090	+10
24·5	20·0	2,900	3,710	1·003	3,720	−820
24·5	20·0	2,700	3,710	1·003	3,720	−1,020
26·4	18·5	3,000	4,160	0·841	3,500	−500
26·6	20·0	3,500	4,210	0·901	3,790	−290
28·3	24·5	3,650	4,510	1·020	4,600	−950
30·9	29·0	5,100	4,820	1·081	5,200	−100
37·2	33·0	4,340	5,120	0·982	5,030	−690

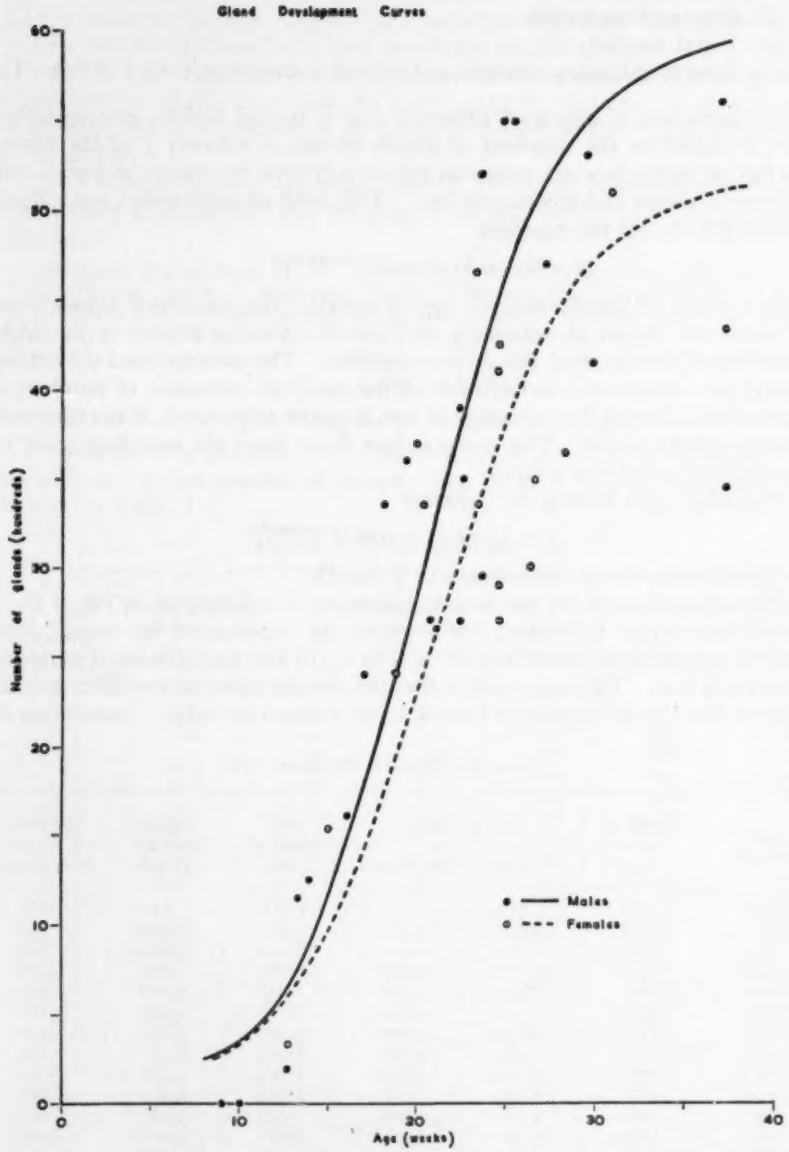

FIG. 1.—Gland Development Curves of the Trachea—for Male and Female Fœtuses.

the data led to the assumptions (which formed the basis of the two curves) that the upper limits were 6,000 for males and 5,200 for females. These are arbitrary values but they are not critical to the shapes of the curves. " Expected " values at 30 weeks are 5,550 for males and 4,750 for females, a difference of 800. It is difficult to estimate the variance to be attached to this difference owing to uncertainty about the exact positions of the upper asymptotes of the curves, but the standard error would be of the order of 900 $(\frac{1}{15}+\frac{1}{15})^{\frac{1}{2}}$ or 300. The difference may very well be just statistically significant, confirming the strong impression of a male superiority in numbers of glands given by Fig. 1. The male and female data have therefore been separated in the following analysis.

Individual Variability in Number of Glands

Before individual variability could be more precisely estimated it was necessary to consider the possible effect of abnormal tracheal length. While length of trachea had been taken as a fourth estimator of age this did not materially reduce the individual deviations from the smoothed curve of variation of tracheal length with age. The ratios of actual (A) to " expected " (E) or trend values for tracheal length as shown in column (5) of Table I were used to adjust the expected glands on the assumption of a linear relationship between tracheal length and total glands. The first value (for age 9·0 weeks), for which no measurement of tracheal length was available, was omitted from this analysis. Column 6 of Table I shows the adjusted " expected " gland values on this basis (retaining a limit of 6,000) and the new residual differences. The variability of the data may then be represented as follows:

Source of variation	*Degrees of freedom*	*Sums of squares*	*Mean*
Regression on age	1	15,003,030	
Regression on length of trachea (age standardised)	1	4,349,000	
Residual	19	13,221,000	695,842
	21	32,573,030	

The revised estimate of the standard deviation of number of glands at a particular age (after adjustment for tracheal length) is 830, as compared with the earlier estimate of 920 (and an unadjusted estimate of 940 for the 22 specimens), a small reduction. Any effect of tracheal length, though probably real, is clearly swamped by individual variability originating from other sources. Any further refinement in the adjustment for tracheal length (*e.g.* by excluding this factor from the estimation of age) is unlikely to alter this general picture.

A similar exercise was carried out for the female specimens and the

appropriate values are shown in Table II. The variances here may be analysed as follows:

Source of variation	*Degrees of freedom*	*Sums of squares*	*Mean*
Regression on age	1	10,719,040	
Regression on length of trachea (age standardised)	1	1,682,100	
Residual	13	8,986,600	691,277
	15	21,387,740	

In this case the initial estimate of the standard deviation of 870 is reduced to 830 (the same value as for males).

It is important to stress the high order of individual variability observed even when age and tracheal length have been taken into account. At 30 weeks of age the expected number of glands for the male trachea is 5,550, but it appears that values as low as 4,000 could be accepted as within the normal range of individual variation. For females at this age, against an expectation of 4,750, it would seem that a value of 3,500 would not be outside the range of variation. In the upward direction it has been assumed that there are limits of 6,000 for males and 5,200 for females and no values were observed above these limits; but the hypothesis does mean that near to the point of completion of the development of glands the distribution of numbers of glands for individual fœtuses would be asymmetrical, stretching out more in a downward direction because of the restrictive effect of the upper limit. It is, however, only a hypothesis suggested by the present data. It does not mean that values higher than 6,000 for males and 5,200 for females will not occur; only that on the present data it seems unlikely. To sum up, the data available indicate that there is a wide individual variation of numbers of glands at maturity; possibly from 4,000-6,000 for males and from 3,500-5,200 for females, though these figures should only be taken as general indications.

Limit of Development of Glands

The inference to be drawn from the data is that further development is insignificant after age 30 weeks by which age 92 per cent. of potential growth has been completed for males and 91 per cent. for females. In fact for both sexes almost seven-eighths of potential growth has been obtained by the twenty-eighth week of age.

It must be borne in mind that precise values of these proportions are influenced by the choice of upper limits in the fitted growth curves of Fig. 1. But they are certainly large and the general impression of virtual completion of growth by about 30 weeks is not likely to be affected by any reasonable upward shift of the asymptotes.

Variation of Tracheal Length With Age

In the course of this analysis two remarkably similar linear equations were derived for the variation of tracheal length with age. These are:

$$\text{Males } y = 1{\cdot}0574x - 5{\cdot}853$$
$$\text{Females } y = 1{\cdot}0744x - 6{\cdot}377$$

where y = length of trachea (mm.) and x = age (weeks).

Noback (1925) produced a formula relating tracheal length in mm. (y) to crown-heel body length in cm. (z):

$$y = 0{\cdot}695\ z + 429$$

The data extend only to 37 weeks of age and extrapolation beyond this point would not be valid.

Table III.—Comparison (Male and Female) of Tracheal Lengths

Age (weeks)	*Estimated values of tracheal length (mm.) according to fitted curves*	
	Males	*Females*
20	15·3	15·1
22	17·4	17·2
24	19·5	19·4
26	21·6	21·6
28	23·8	23·7
30	25·9	25·9
32	28·0	28·0
34	30·1	30·2
36	32·2	32·3

Specimen values for these curves are shown in Table III from which it is clear that age for age the male and female tracheas are estimated to have almost exactly the same length. The difference in total glands already referred to cannot therefore be explained in terms of different tracheal lengths. The explanation must lie entirely in differing concentration of glands. This may be illustrated by the following figures (for the older fœtuses) taken from the basic data.

In general at ages older than 24 weeks the male gland concentration is higher than for females. It was earlier suggested that the male excess in total glands at these ages is of the order of 20 per cent. The difference in gland concentration shown in Table IV appears to be consistent, as the excess of glands in the male can be fully explained by higher concentration.

This confirms that the difference between the number of glands in male and female tracheas results from the difference in concentration of glands rather than from the absolute size of the trachea.

TABLE IV.—CONCENTRATION OF GLANDS—NUMBER PER 7 μ SECTION

Age (weeks)	*Males*		*Age (weeks)*	*Females*	
	Glands per 7 μ section			*Glands per 7 μ section*	
	Observed values	*Mean ± s.e.*		*Observed values*	*Mean ± s.e.*
20·7	1·73		20·3	1·79	
21·0	2·00				
22·3	1·37				
22·3	1·84				
22·5	1·87				
23·5	1·46		23·3	1·88	
23·5	2·18		23·3	2·13	
20-24		1·78 ± 0·10	20-24		1·93 ±0·10
24·9	2·24		24·5	1·81	
			24·5	1·85	
			24·5	1·28	
25·6	2·13		26·4	1·52	
27·2	1·86		26·6	1·54	
24-28		2·08 ±0·11	24-28		1·60 ±0·11
29·5	1·57		28·3	1·57	
29·8	1·15		30·9	1·55	
28-32		1·36 ±0·21	28-32		1·56 ±0·01
37·0	1·55				
37·2	0·86		37·2	1·01	
32-		1·21 ±0·34	32-		1·01

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INTRACAVITARY FUNGUS BALLS IN PULMONARY ASPERGILLOSIS

By Alex Saliba, Luigi Pacini and Oren A. Beatty

From the District Two State Tuberculosis Hospital, Louisville, Kentucky

Mycotic infections continue to play an increasingly important rôle in the practice of medicine, and often present a challenge in the speciality of pulmonary diseases. Although a relatively new field, one finds reports on the mycoses more frequently in medical literature. An increase in these infections may be the result of an indiscriminate use of antibiotics and increasing use of the corticosteroids.

Aspergillus species commonly occur in nature as saprophytes, and are a frequent contaminant in the laboratory. Some are pathogenic, notably *A. fumigatus*; other species have also been recorded as causing disease infrequently. *M. tuberculosis* or *H. capsulatum* is not always the ætiological agent of cavitary pulmonary disease. Other mycotic infections produce a similar picture, and particularly, several cases of aspergillosis have been reported, some with a typical "cavitary fungus ball." Levin (1956) records 27 such cases, 18 of which were proved by microscopy, the organism most commonly isolated being *A. fumigatus*. A common finding in these cases was hæmoptysis, and there were no acid-fast bacilli in the sputum.

We are reporting three cases of pulmonary aspergillosis with the typical fungus ball appearance. This was obvious in the roentgenograms of two patients, and was found on examination of the surgical specimen of the third. Two of these patients had resection of the lesion and a short course of Amphotericin-B intravenously. One case presented with bilateral apical cavities, in which the fungus mass could be distinctly identified. This appears to be the first case of bilateral apical "fungus balls" reported. Three other cases are briefly mentioned—the pathological report having suggested the presence of aspergillosis.

Case Histories

Case 1. J.B. was a 69-year-old farmer. He had kept chickens and often cleaned out the chicken houses. He first developed symptoms in January 1960, with an influenza-like illness and a productive cough. For two years he had noticed weakness and lethargy. Small hæmoptyses had occurred on three occasions. On examination amphoric breathing with occasional râles were noted over both apices. The breath sounds were decreased at the bases.

A chest X-ray showed an infiltrative process throughout both lung fields, but mostly in the upper lobes. There was evidence of emphysema. Large cavities were present at both apices, and within each there was a dense round mass, which was better visualised on tomography (Figs. 1-2). A few weeks after admission the patient developed signs of cor pulmonale; because of this

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and the emphysematous changes, as well as the bilateral nature of the disease, surgery could not be considered.

A diagnosis of aspergillosis was suggested on roentgenography and aspergilli were isolated on several occasions from sputum. This was also obtained in pure culture from intracavitary aspiration of material. Skin testing and sputum examinations were negative for tuberculosis, histoplasmosis and other fungi.

Under local anæsthesia a needle was inserted posteriorly into the left apical cavity, an adherent thickened pleura was encountered. Inside the cavity atmospheric pressures were recorded indicating open bronchial communication—this is relevant, as repeated examination of the copious sputum failed to yield any acid-fast bacilli or any fungi except aspergillus. The needle was inserted until contact with the mass was suspected and flecks of material were aspirated and cultured on plates of Sabouraud's dextrose agar. Some normal saline was introduced and further aspiration carried out for purpose of animal inoculation. Finally 2 ml. of oily Dionosil were injected and a multilocular type of cavity was revealed, the opaque medium clearly defining a 3 cm. fungus mass. Communicating bronchi were demonstrated.

Within three days at room temperature the plates inoculated with material from the left apical cavity contained pure growths of fluffy white mycelia. By eight days there was an abundant growth in pure culture turning green in colour, and on microscopy hyphæ and conidiophores typical of aspergillus were readily identified (Fig. 3).

Case 2. L.P. was a 37-year-old woman who was first diagnosed as having "tuberculosis" in 1943, following the onset of respiratory symptoms and hæmoptysis. She had collapse therapy and subsequently antimicrobials in different combinations. In 1952 two concentrated sputum smears were reported positive for acid-fast bacilli, cultures not being available, and this was the only bacteriological evidence suggesting tuberculosis. In September 1952 a left upper lobectomy (Figs. 4-5) was carried out in another hospital, with a pathological diagnosis of tuberculosis. Following this, she was admitted to our hospital for further treatment and convalescence before discharge. She was readmitted in 1957 with a chest roentgenogram showing a residual air pocket (post-operative) in the left apex and evidence of progressing disease on the right (Fig. 6). Tomograms of 20.3.57 showed a round lesion capped by an air crescent in the right mid lung field suggestive of an aspergilloma (Fig. 7). A resection of the right upper lobe and apical segment of right lower lobe was carried out on 17.4.58 when a pathological diagnosis of aspergillosis was made; the pathologist made no reference to any definite tuberculous lesions. She had a short course of Amphotericin-B therapy as this drug was poorly tolerated, and she also remained on anti-tuberculous drug therapy. Numerous sputum examinations were negative by smear and culture for acid-fast bacilli. When last seen on 26.7.60 she was feeling well, with no signs of active disease on roentgenogram.

Case 3. A 48-year-old woman had been under treatment for respiratory complaints for two years. She was having repeated hæmoptyses and her general condition was deteriorating. Initially the tuberculin and histoplasmin skin sensitivity reactions were negative; later, a repeat PPD was found positive. Complement fixation reaction for fungi was reported positive for histoplasmosis

PLATE IX.

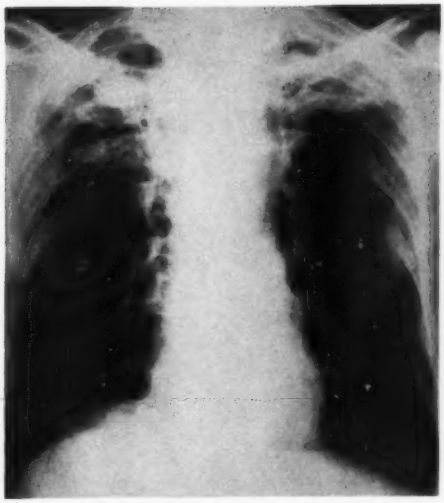

FIG. 1.—Roentgenogram of May 1960 showing an infiltrative process mostly in both upper lobes and findings of emphysema. Bilateral apical cavities are clearly seen, containing an indistinct fungus mass.

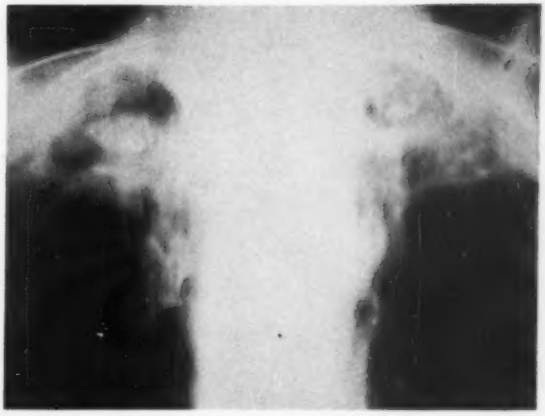

FIG 2.—AP tomogram confirming presence of intracavity fungus balls in both upper lobes.

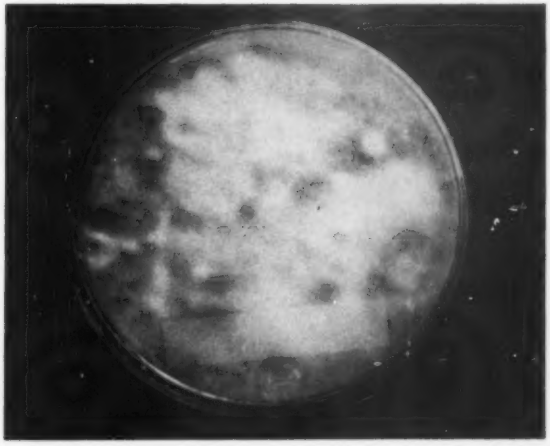

FIG. 3.—Culture from aspirated contents from left apical cavity contained an overwhelming growth of Aspergillus, considered here a pathogen, with typical microscopic findings at 8 days culture at room temperature. This was subcultured as seen in the above when the same overwhelming growth was obtained, the colonies turning greenish within eight days.

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PLATE X.

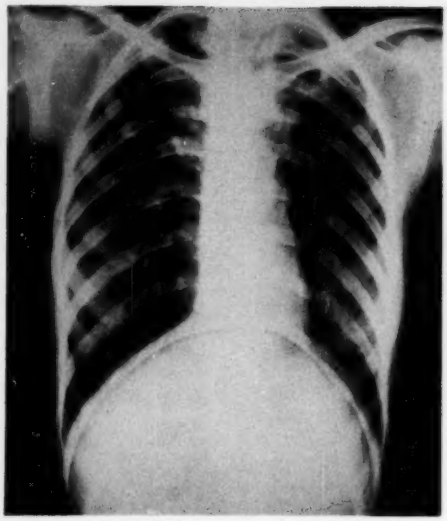
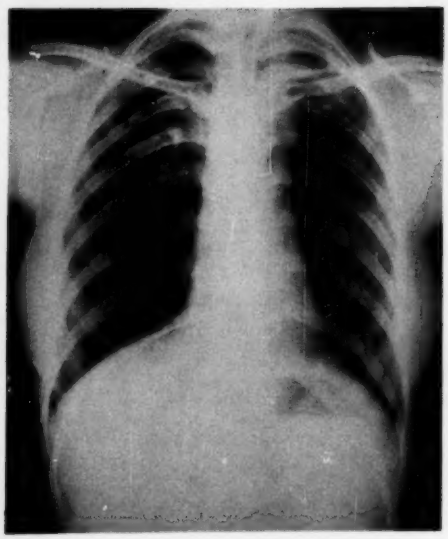


FIG. 4.—PA chest X-ray of June 1952 showing cavitary disease in the left upper lobe with moderate infiltration in right upper lobe. An indistinct thin walled cavity is also seen in the apical segment of right lower lobe.

FIG. 5.—Tomogram of July 1952 clearly outlines the contracted, excavated left upper lobe, with the contralateral infiltrative process in the right upper lobe.



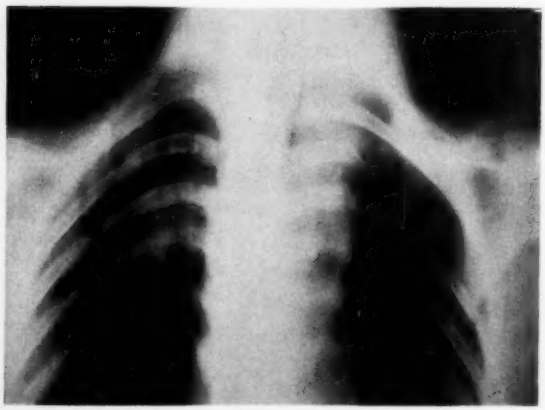


FIG. 6.—PA chest roentgenogram of March 1957 showing evidence of resectional surgery on the left, with a small residual apical air pocket. On the right is seen the infiltration in the contracted RUL with the fungus mass capped by an air crescent in the apex of right lower lobe.

FIG. 7.—AP tomogram outlining the intracavitary fungus ball in the apical segment of right lower lobe.

on two occasions, out of four examinations. Sputum examinations were repeatedly negative by smear and culture for tuberculosis, and also for fungi apart from three tests reported positive for *A. fumigatus*.

The patient was transferred to our hospital on 5.3.59 for surgery. Chest X-ray showed a destroyed left lung with multilocular cavities, and minimal infiltration in the right upper lobe. She was put on Amphotericin-B intravenously three times a week, and on 18.6.59 a left pneumonectomy was carried out. The post-operative course was uneventful and her general condition improved. Amphotericin-B was given for a total dosage of 273·3 mg. when it was discontinued. The pathological diagnosis was " tuberculous nodules with fibrosis and aspergillosis."

Cases 4, 5, 6. These three patients had a pathological diagnosis of aspergilloma in surgical specimens. Two cases originally had sputum cultures positive for tuberculosis; and in one patient the examinations were repeatedly negative for tuberculosis. In one case no tomograms were available; in the other two, tomograms showed no characteristic appearance of a " fungus ball " in one case and a typical appearance in the other. Again, two of these cases had complained of intermittent small hæmoptyses.

Comment

Case number 1 is considered a primary infection with aspergillus which presented with bilateral apical cavities containing fungus balls. Aspiration of material from the cavity assisted the diagnosis. An overwhelmingly pure culture of the organism was isolated from a subculture of sputum as well as from the contents of the cavity. Case number 2 was a case of aspergillosis superimposed on pulmonary tuberculosis, but there was no absolute bacteriological proof of the latter. Also, the pathological diagnosis following the second operation mentions aspergillosis with no reference to definite tuberculous lesions. Case number 3 had a pathological diagnosis of tuberculous nodules and aspergillosis, but repeated examinations revealed no acid-fast bacilli. On the other hand, a positive complement fixation reaction for histoplasmosis, on one occasion as high as 1/128, would suggest the possibility that *H. capsulatum*, if not properly looked for, could have been missed on the surgical specimen. Thus this could have been a case of aspergillosis superimposed on histoplasmosis, though the latter organism was not identified.

Of the remaining three patients two had pulmonary tuberculosis and aspergillosis as bacteriological proof of tuberculosis was present. The other case was apparently one of primary aspergillosis. The disease was principally in the upper lobes in four out of six patients. With tomography intracavitary fungus balls were readily identified in three cases. A varying degree of hæmoptysis was a main presenting feature in five of these cases. In five the diagnosis of aspergillosis was made on surgical specimen; and in the case with bilateral intracavitary fungus balls, aspirated cavity contents confirmed it.

Discussion

The pulmonary mycoses are receiving more attention, and histoplasmosis is perhaps the best known because of series of cases reported by several

investigators. Most of these have been in the U.S., but sporadic cases have been diagnosed in most countries, not necessarily in people who had travelled outside the boundaries of these countries. Furcolow and Brasher (1956) drew particular attention to the similarity between chronic histoplasmosis and tuberculosis and hence its importance for tuberculosis sanatoria. Indeed, Procknow and Loewen (1960) point out that many of these hospitals can now pride themselves on the ability to differentiate between tuberculosis and histoplasmosis. Aspergillosis, too, has been reported from many countries, and the cavitary form can be confused with tuberculosis and with histoplasmosis and other chronic pulmonary conditions.

The isolation of the infecting organism, by no means easy in the mycoses, is essential for a definite diagnosis, and much time is usually involved. The writers have pointed out the difficulties of such a diagnosis in the case of histoplasmosis, even from the pathological aspect (Saliba and Beatty, 1960). Unfortunately there are no typical X-ray findings, but paratracheal glands, calcified or otherwise, have often been found in histoplasmosis infection. This, correlated with more disseminated calcification, fibrosis and compensatory emphysema, may suggest the diagnosis.

Roentgenographic appearances can be more helpful in cavitary aspergillosis because of the common occurrence of a " fungus ball." This is seen as a rounded density capped or surrounded by an air translucency. Mobility of this mass can be significant. Vellios and others (1957) note that this description was first used by Deve in 1938. Weens *et al.* (1950) state that this air crescent was once considered pathognomonic of echinococcus or hydatid cysts. This differs from aspergillosis because of the mobility of the mass in the latter. Pesle and Monod (1954) maintain that roentgenographic appearances are characteristic enough to suggest a diagnosis of aspergillosis, and they state that the air crescent is always thin, and much smaller than the enclosed fungus ball. This contrasts with our first case where the small mass can be seen surrounded by a larger air translucency. These authors also suggest the probability that fungus infection precedes the development of bronchiectasis.

The consensus of opinion is that the organism in aspergillosis invades pre-existing areas of disease such as tuberculosis, congenital cysts, carcinoma, bronchiectasis, etc. Primary aspergillosis has been known to occur and Smith Foushee *et al.* (1958) mention a few cases recorded in the literature and report a case of primary cavitary aspergillosis limited to the right upper lobe and treated by lobectomy. At the other extreme there may be rapid dissemination of the disease with fatal results as described by Toigo (1960).

Symptoms vary, the commonest is a productive cough. Hæmoptysis of a varying degree is frequent. Sputum examinations are often negative for tuberculosis and tuberculin skin sensitivity may also prove negative. A preparation from a patient's positive sputum culture for aspergillosis may be used for a specific intradermal test, and this reaction is usually markedly positive. The " fungus ball " consists of intertwined mycelia and usually lies free in the cavity. It can occupy from one-fourth to most of the volume of the cavity. Calcification has occasionally been reported. The lesions are more

often in the upper lobes and sometimes in the apical segments of the lower lobes. Cultures from material taken from surgical specimens have often been reported negative. This is attributed to the presence of a large number of non-viable organisms within the mass.

Yesner and Hurwitz (1950) have distinguished the following type of pulmonary aspergillosis: (*a*) acute pneumonic and generalised, (*b*) mild and benign, (*c*) chronic cavitary. The latter could be indistinguishable from tuberculosis or histoplasmosis and could coexist with either condition.

Pepys *et al.* (1959) reported on the greater frequency with which they isolated *A. fumigatus* from sputum of asthmatic patients. This taken in conjunction with other tests confirmed the presence of hypersensitivity to this fungus. They suggest there may be a close association between presence of *A. fumigatus* in sputum, precipitins in serum, positive skin test reactions and pulmonary infiltrations. Plummer (1960) referred to the relatively good prognosis of the allergic type in a study of 85 cases of pulmonary aspergillosis. He was of the opinion that the organism behaved principally as a saprophyte and believed that the simple variety of mycetoma (in a simple cyst) was a better surgical risk than the complicated form. Orie *et al.* (1960) reporting on 51 cases of pulmonary aspergillosis confirms evidence of pre-existing disease in at least 44 and ascribes to this most of the manifestations presented by patients.

Therapy remains a problem. Belcher and Plummer (1961) in a review of 21 cases report a morbidity of 75% following surgery for complex aspergillomas and aspergillus infection in suppurative lesions. In contrast there were few complications in cases of simple aspergillomas. They also pointed out that post-operative complications developed in all but one of their cases in whom the fungus had previously been isolated from sputum. The authors suggest that surgery should be avoided in allergic aspergillosis, and when possible in complex aspergillomas and aspergillosis in pulmonary suppuration; on the other hand, surgery is much safer in simple aspergillomas. The higher morbidity referred to above has been attributed mostly to the underlying disease and secondary bacterial infection. However, other authors as Smith Foushee (1958), Yesner (1950), Friedman (1956), Gerstl (1948), Hughes (1956), Hausmann (1958), and their colleagues have reported that resection for localised lesions of aspergillosis has proved a satisfactory form of treatment. Many of these cases would be classified as simple aspergillomas as mentioned by Belcher and Plummer.

A comparison may be made with a study by the present writers dealing with surgery in pulmonary histoplasmosis. Those patients who received Amphotericin-B concomitantly or very soon after surgery showed a low incidence of complications; whereas without Amphotericin, surgery carried a high morbidity such as bronchopleural fistula and pneumonic spread. Thus the use of an antimycotic agent in aspergillosis may also reduce post-operative complications.

In a review of therapy Procknow and Loosli point out that whereas Amphotericin-B has proved itself useful in histoplasmosis, this was doubtful in aspergillosis, although encouraging results have been reported and further

evaluation is indicated. Iodides, nystatin and a number of other agents have been tried with uncertain results. They say that surgery appears to be the treatment of choice for localised disease. The addition of an effective antimycotic may reduce the risk of complications. A study of the morbidity in the present series confirms the findings of Belcher and Plummer. Of the five cases surgically treated, one developed a bronchopleural fistula managed conservatively, one showed a transient pneumonic spread to the opposite lung, and one died post-operatively. None of these cases would be classified as " simple aspergillomas." The patient with the fistula is one of those who received a short course of Amphotericin-B; this however was not given until some four and a half months after operation.

In conclusion pulmonary aspergillosis can present as a primary or secondary infection, with localised lesions or with progression and dissemination to most organs proving fatal. It can occur at all ages and Cawley (1946) has described the fatal course of the illness in a child under three years old. Medical treatment has been disappointing, although Amphotericin-B needs further evaluation. Surgery has been successful for some cases of localised disease and the concomitant use of an effective antifungal agent may reduce morbidity in all forms of aspergillosis.

Summary

A brief discussion is presented with regard to pulmonary aspergillosis as a primary or a secondary infection. Reference is made to the characteristic roentgenographic appearance of the intracavitary fungus ball, and to the importance of isolating the organism directly from lung material, rather than sputum. Intracavitary aspiration can prove useful.

Six cases are presented, the first three in some detail. The first case has bilateral apical cavities with fungus balls, the only case of this type apparently reported in the literature. Tomography is useful in readily identifying the fungus mass surrounded by the air crescent. Resectional surgery has been a successful form of therapy for the localised form of the disease. Amphotericin-B has received encouraging reports and needs further evaluation.

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INCREASED TRANSRADIANCY OF ONE LUNG

By Desmond J. Leahy

From Walsall General (Sister Dora) Hospital

Introduction

A group of cases recognised on clinical examination by diminished breath sounds over one lung and by decreased movements of the chest wall on the same side has been described by Macleod (1954). X-ray examination shows increased transradiancy of the affected lung and diminished hilar and vascular shadows. Fluoroscopy reveals a picture similar to that of obstructive emphysema; there is diminished excursion of the affected lung and deviation of the mediastinum towards the normal side on expiration. Bronchoscopy and bronchography, however, reveal no evidence of obstruction in the major bronchi, but bronchography does reveal an abnormality of the peripheral bronchi, either of the whole lung or of one or more lobes. Pulmonary function studies characteristically reveal diminished ventilation and markedly diminished oxygen uptake in the affected lung or in one or more lobes. Angiograms show that the pulmonary artery is reduced in size. The whole vessel may be involved or only the lobar branches (Belcher and Pattinson, 1957; Belcher *et al.*, 1959). This syndrome has been variously described as: abnormal transradiancy of one lung, increased transradiancy of one lung, unilateral pulmonary " emphysema," hypoplasia of the pulmonary artery and idiopathic unilateral hyperlucent lung. Each title is descriptive of one or more aspects of the syndrome. It might be noted that the word " translucent " refers to light, " transradiant " would therefore be a more correct term when referring to X-rays. Hypoplasia of the pulmonary artery is the title favoured by Belcher *et al.* (1960). They object to the term unilateral emphysema on the grounds that there is in fact no true emphysema.

Two new cases of the syndrome are reported in this paper and their investigations are described. A brief history of both cases is given below. The previous history is considered to be of importance in that it throws light on the possible ætiology of the condition.

Case Histories

Case 1. A well-built muscular man of 35 years, employed as a railway worker, complained of increasing exertional dyspnœa over the past five years. Recently the dyspnœa had become more marked and the patient now had difficulty in carrying on his work. His previous history showed that he had had " pneumonia " twice at the age of 6 and 12 years. On examination there was no cyanosis or clubbing. Both sides of the chest were well developed. The left side of the chest moved less than the right side. The most notable feature of the clinical examination was the markedly diminished breath sounds over the left lung.

CASE 2. A well-built man of 22 years, who was referred for examination following an attack of influenza. He did not suffer from exertional dyspnœa, but on clinical examination he had diminished breath sounds over the left lung; no other abnormality was noted. At the age of 2 years he developed a severe chest infection and was admitted to the Manor Hospital, Walsall, where he remained for twenty-two weeks. From the details of the illness given to his mother it would seem that his lung was collapsed at that time for a prolonged period.

INVESTIGATIONS AND RESULTS

The results of radiological examination of cases 1 and 2 are recorded in Table I and the chest radiograph and bronchogram of case 1 are shown in Figs. 1 and 2.

An investigation of the pulmonary function, including differential pulmonary function of case 1, was undertaken at the Postgraduate Medical School by Dr. P. Hugh-Jones and Dr. J. B. West.

TABLE I.—RESULTS OF RADIOGRAPHIC EXAMINATION AND FLUOROSCOPY IN TWO PATIENTS WITH INCREASED TRANSRADIANCY OF ONE LUNG

Case No.	*Lung affected*	*Lobes affected*	*P.A. chest radiograph*	*Fluoroscopy*	*Bronchography of left lung*
1	Left	All lobes	Increased transradiancy of left lung. Small hilar pulmonary artery shadow. Diminished vascular markings in lung field. The right lung was normal.	The resting mediastinal position was central. Mediastinal deviation towards and into the normal side on expiration was well marked. The left hemidiaphragm shows diminished movement on inspiration and expiration.	The major bronchi outlined normally. No evidence of obstruction was seen. All segmental bronchi were present and filled. Absence of filling in the finer bronchial radicles was a marked feature, also irregularity in shape and size. Terminal "clubbing" was noted, also beading and cylindrical diminution or increase in size. Small loculi of oil were seen attached to some of the bronchi.
2	Left	Lower and Lingula	Increased transradiancy of the left lung was noted. The left hilar shadow and pulmonary markings were diminished. The right lung was normal.	The resting mediastinal position was central. On expiration the contrast between the two lungs became more marked. The mediastinum moved towards the normal side on full expiration.	The major bronchi outlined normally and no evidence of obstruction was seen. Bronchiectatic dilatations involving the whole lower lobe and lingula were noted. There was no peripheral filling in the affected lobes.

TABLE II.—CASE 1. PULMONARY FUNCTION TESTS IN PATIENT WITH INCREASED TRANSRADIANCY OF ONE LUNG

Co. diffusing capacity	*Total lung capacity (litres)*	*Funct. residual capacity (litres)*	*Residual volume (litres)*	*R.V. T.L.C. ratio*	*Ind. M.B.C. l./min.*	*F.E.V. l./sec. (litres)*	*F.V.C. (litres)*	*V.C. (litres)*	*F.E.V. V.C. ratio*
At lower limits of normal	4·69	2·28	1·90	40%	47 (57)	1·33 (1·63)	2·35 (2·63)	2·59 (3·08)	51% 53%

Figures in parentheses represent values after 5 mins. 1% isoprenaline.

Pulmonary function studies (Table II) revealed that: the ratio of residual volume to total lung capacity was much increased (normal ratio at 35 years is 20 to 25 per cent.). The maximum breathing capacity as measured indirectly from the forced expiratory volume in 1 second (F.E.V. 1·0) was considerably reduced (normal values 100-160 litres per minute). The ratio of the forced expiratory volume 1 second value to the vital capacity was low; it should be 75 to 80 per cent. Differential pulmonary function was investigated by a method using radioactive oxygen (0-15) (Dyson *et al.*, 1958; Dyson *et al.*, 1960). The results are summarised in Table III.

TABLE III.—CASE 1. DIFFERENTIAL PULMONARY FUNCTION TESTS IN A PATIENT WITH INCREASED TRANSRADIANCY OF ONE LUNG

	Right lung	*Left lung*
Ventilation	Normal	33% of right lung.
O_2 Uptake	Normal	Practically nil.
Perfusion	Normal	Practically nil.

Radioactive O_2 was used to determine these values.

The method used was as follows: the patient breathes air in and out of a spirometer, during an expiration radioactive oxygen is added to the system; on the subsequent inspiration the patient takes up to one litre of active air. The breath is now held for 10 seconds, then normal breathing is resumed. The expired active air is led to waste. The tracing obtained (Fig. 3) is explained as follows: the initial height of the curve is proportional to the ventilation and the slope of the curve during breath holding is proportional to the blood flow, being chiefly determined by the clearance of radioactive oxygen in the blood. The right lung tracing shows a normal initial upswing followed by a normal decline during breath holding (= normal ventilation, oxygen uptake, and perfusion). In the left lung tracing the initial deflection is low and the decline during breath holding is almost nil (= diminished ventilation and very low values for oxygen uptake, and perfusion). The low oxygen uptake is not due to a diffusion defect as the pulmonary diffusing capacity determined by the carbon monoxide method was within normal limits (Table II).

PLATE XI.

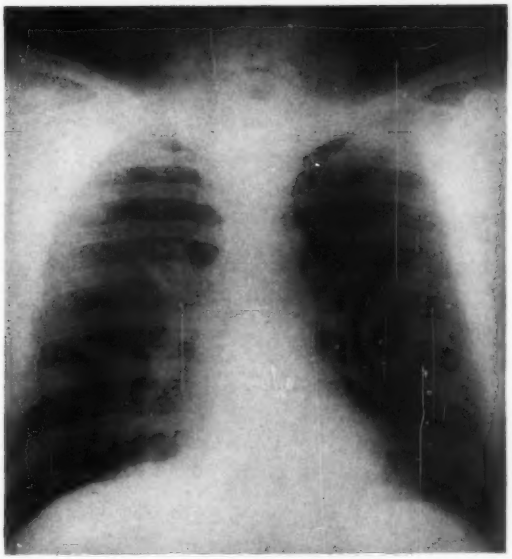

FIG. 1.—Case 1. Postero-anterior radiograph showing increased transradiancy of the left lung.

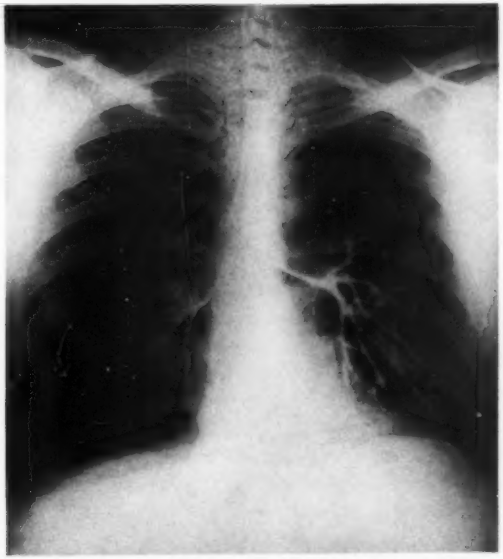

FIG. 2.—Case 1. Bronchogram of left lung showing characteristic features. (See Table 1.)

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PLATE XII.

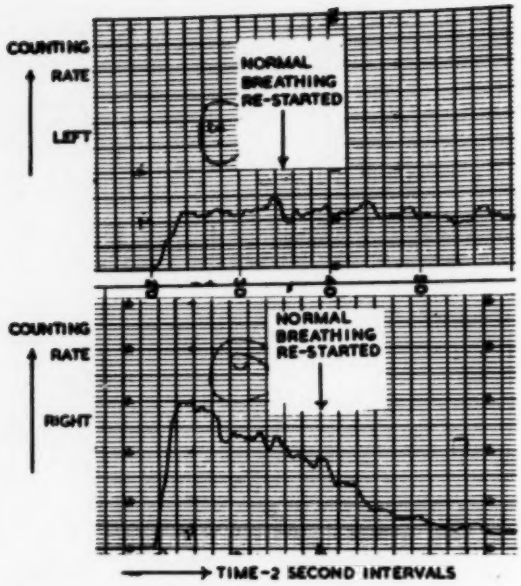

FIG. 3.—Case 1. Differential pulmonary function investigation. Radio-active oxygen tracings from patient with Increased Transradiancy of One Lung. [Reproduced from Dyson *et al.* (1958)]

Discussion

Both cases reveal the characteristic clinical and radiological features of this syndrome as described in the opening paragraph and as set forth in previous series (Table IV). The physiological findings of increased residual volume and decreased forced expiratory volume with decreased ventilation and markedly decreased oxygen uptake and perfusion are typical of the values reported in the other series.

A high incidence of " pneumonia " in early life has been noted in previous series; the cases now reported are typical in this respect. Case 2 is particularly interesting in that the lung was apparently collapsed for a prolonged period.

TABLE IV.—PREVIOUS SERIES OF CASES REPORTED OF INCREASED TRANSRADIANCY OF ONE LUNG INCLUDING OPERATIONS PERFORMED

Author	*Date*	*No. reported*	*Operation*
Swyer and James ..	1953	1	Pneumonectomy 1 case
Macleod	1954	9	
Belcher and Pattinson ..	1957	3	
Dornhorst *et al.*	1959	4	
Belcher *et al.*	1959	13	Pneumonectomy 2 cases
Katz and Wagner ..	1959	1	
Margolin *et al.*	1960	4	
Fouché *et al.*	1960	7	
Present series	1960	2	Pneumonectomy 1 case

In two of Margolin's cases there was a history of foreign body aspiration with presumably lung collapse (Margolin *et al.*, 1959). The inference is that the lung suffers damage in childhood, many of the alveoli and respiratory bronchioles being damaged or destroyed in the affected lung. The lung, however, develops to normal or almost normal size. The diminished vascularity of the lung is generally considered to be secondary to the low functional capacity of the lung.

These cases usually run a benign course and may continue for years without alteration. There appears to be no increased susceptibility of these abnormal lungs to infection, as occurs usually in bronchiectasis. The author would like to suggest that this is due to the fact that these lungs are usually " dry," no doubt due to the injury the lung received in early life.

Treatment depends on the extent of the disability. If dyspnœa is increasing and is of such a degree that work is impossible, and if there is air trapping and mediastinal deviation, then pneumonectomy or lobectomy should be considered. This stage was reached by case 1 and pneumonectomy was performed with excellent results. The patient is now fit and well and working full time. Case 2 had no symptoms and required no treatment. Pneumonectomy was performed in two of Belcher *et al.*'s cases, one patient being greatly improved and the other slightly (Belcher *et al.*, 1959). One of Margolin's cases had a right lower lobectomy with considerable improvement (Margolin *et al.*, 1959).

The success of pneumonectomy is due to the removal of a lung which is not only functionless but is also causing mediastinal deviation and so actively interfering with the function of the normal lung. The mediastinal deviation is due to air trapping in the abnormal lung.

Summary

Two new cases of increased transradiancy of one lung are reported and their clinical and radiological features described. In one case the results of lung function tests are given, including the results of differential lung function investigations carried out by radioactive oxygen.

One patient, a man of 35 years, complained of increasing exertional dyspnœa, which rendered work impossible; pneumonectomy was performed with excellent results. The other patient, a man of 22 years, did not suffer from dyspnœa, but had the clinical and radiological signs of the syndrome.

A history of " chest illness " in childhood was definite in both cases and is considered to be a causative factor, especially in view of the very frequent history of chest illness reported in other series.

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THE SURGICAL TREATMENT OF ASTHMA

By J. R. Belcher

From the London Chest Hospital

Has surgery a place in the treatment of asthma? This investigation was based on the assumption that it had. Papers by Phillips and Scott (1929), Reinhof and Gay (1938), Klassen and others (1950), Blades and others (1950), Abbott and others (1950), and more recently by Szokodi (1957) and by Overholt (1959), all maintained that a proportion of patients treated by operations on the splanchnic nerves supplying the lungs were greatly improved. This paper is a report on a series of sixteen cases in which the sympathetic and the parasympathetic nerve supply to the right lung was divided. A further attempt has been made to assess the results of this procedure.

The Patients

All save one of the sixteen patients under review were treated at the London Chest Hospital. They had an average age of 48·5 years with extremes of 23 and 70; 11 were men and 5 were women.

In all the disability was severe, although the wide variation of presentation so characteristic of the disease was seen. Some of the patients had occasional very severe attacks of status asthmaticus, while, at the other end of the scale, some were seldom free of a " wheeze " (Table I). All except one had been under treatment for more than two years, and in three the history extended over more than twenty years. Most had had the usual wide variety of therapy, and fifteen had had steroids at one time or another. None of the men had been able to maintain steady employment, and three of the five women had had attacks so severe as to necessitate frequent admission to hospital. All were sufficiently disabled to accept surgery, although they were aware of the uncertainty of the long-term results.

Selection of Cases

No operation on the splanchnic nervous system can hope to lessen pre-existing lung damage, but although asthma may eventually lead to lung destruction, it may be lethal before there are any obvious pulmonary lesions.

As far as possible, patients suffering from pure asthma were chosen for operation, and those suffering from chronic bronchitis and from emphysema were excluded as it was thought that surgery was unlikely to improve them. Patients whose dyspnœa was due to large emphysematous cysts were also excluded. Consistent good results are obtained when these bullæ are removed (Capel and Belcher, 1957), whether or not they are subjected to vagotomy at the same time. The improvement is due to the removal of mechanical

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interference with respiration. Lastly, no case in which any form of pulmonary resection was done was included.

It was thought that if these three groups were excluded, it might be easier to ascertain the place of posterior pulmonary plexus resection in the treatment of pure asthma. The selection was successful in that only three of the sixteen patients under review had macroscopic evidence of emphysema at operation.

All except one of the patients had had steroid therapy in one form or another (Table I). In some this had been continued for a long time. In four patients complications had supervened: in two hæmatemeses made it necessary to discontinue prednisone altogether; in another a gastric ulcer developed, and

TABLE I

No.	*Age*	*Sex*	*History*	*Disability*	*Steroids*
1	45	M.	13 years	Severe; 4 months per year in hospital	20 mg. prednisone per day before operation.
2	49	M.	20 years	Almost continuous wheeze with exacerbations	None.
3	55	M.	5 years	Severe: almost continuous wheeze	Periodical prednisone, none at operation.
4	42	F.	25 years	Frequent severe attacks	ACTH 20 U. daily at operation.
5	55	M.	25 years	Almost continuous wheeze. *Gastric ulcer*	10 mg. prednisone daily at operation.
6	51	M.	3 years	Frequent severe attacks. *Hæmatemesis*	15 mg. daily. Stopped before operation.
7	44	M.	4 years	Frequent moderate attacks. *Moon facies*	Cortisone 25 mg. daily at operation.
8	70	M.	4 months	Frequent very severe attacks. *S.R.*	20 mg. prednisone daily at operation.
9	55	F.	9 years	Infrequent very severe attacks	ACTH 10 U. daily at operation.
10	63	F.	3 years	Almost continuous wheeze. *Hæmatemesis. S.R.*	20 mg. prednisone daily at operation.
11	46	M.	4 years	Frequent severe attacks. *S.R.*	20 mg. prednisone daily at operation.
12	23	F.	8 years	Frequent severe attacks	15 mg. prednisolone daily at operation.
13	43	F.	6 years	Occasional very severe attacks	Periodical prednisone not at operation.
14	38	M.	2 years	Frequent very severe attacks	25 mg. cortisone daily at operation.
15	52	M.	3 years	Frequent severe attacks	20 mg. prednisone daily at operation.
16	53	M.	1 year	Frequent severe attacks. *S.R.*	30 mg. dexamethozone daily at operation.

although the drug had given dramatic relief of his asthma, it had to be stopped. Another developed a marked " moon facies " after four years' treatment with prednisone.

In eight patients the dose of prednisone or its equivalent was high (15 mg. or more daily), and it was thought that this could not be continued indefinitely. In some of these the drug, after initial success, had become ineffective.

History

An attempt was made to distinguish asthma from bronchitis from the history. Three points were especially looked for: first, although asthma is frequently associated with a productive cough, the sputum is seldom purulent; in bronchitis it is purulent at times. Only three of the sixteen patients gave a history of purulent sputum, and in these the symptom was infrequent. Secondly, the history of the dyspnœa seemed important; clearly, no operation was likely to give relief greater than that which was enjoyed during the remissions, but those patients in this series who had widely spaced attacks had little dyspnœa between them. On the other hand, those who had an almost continuous " wheeze " were more difficult to assess as they gave a history much more like that of the chronic breathlessness associated with severe bronchitis. Lastly, and perhaps most important, the history of the remissions themselves which was given by all but four of the patients helped to differentiate the " asthmatics " and the " bronchitics."

Respiratory Function Tests

It was hoped that the standard respiratory function tests might help to differentiate between asthma and bronchitis. In each patient estimations were made of the F.V.C., the F.E.V.I., and the F.E.R. (Capel and Smart, 1958). In some these estimations were made on a number of occasions. Table II shows the results of these tests done immediately before operation.

Table II

No.	*F.V.C.*	*F.E.V.I.*	*F.E.R.*
1	2,000 c.c.	800 c.c.	40%
2	2,900 c.c.	1,100 c.c.	38%
3	1,800 c.c.	900 c.c.	50%
4	2,700 c.c.	1,600 c.c.	59%
5	3,200 c.c.	1,600 c.c.	50%
6	3,300 c.c.	1,200 c.c.	36%
7	2,900 c.c.	1,200 c.c.	41%
8	2,800 c.c.	1,300 c.c.	46%
9	2,100 c.c.	1,300 c.c.	62%
10	1,100 c.c.	400 c.c.	36%
11	3,000 c.c.	1,000 c.c.	33%
12	1,500 c.c.	900 c.c.	60%
13	1,400 c.c.	500 c.c.	36%
14	3,700 c.c.	2,700 c.c.	73%
15	3,800 c.c.	1,600 c.c.	42%
16	2,000 c.c.	1,000 c.c.	50%

All three figures varied widely from case to case; in some they were almost normal. whereas in others they showed considerable reduction from the usual values. The F.E.V.I. was less than 1,000 c.c. in five patients, but was well above the level at which even moderate dyspnœa is experienced in four. The F.E.R. was considerably lowered in more than half the patients, but in none

was it below the level (30 per cent.) which indicates severe obstructive airway disease. The F.V.C. varied between 1,100 c.c. and 3,700 c.c. with an average of 2,500 c.c.

In those patients who had a number of tests done, the wide variation from day to day which is so characteristic of asthma was often seen. This variation is the factor which makes it impossible to assess a case from a single session, nevertheless it is helpful in that it is characteristic of the disease and is not seen when the lungs are emphysematous.

Finally, it was hoped that the response to adrenaline might be helpful in predicting the possible result of surgery. This was not found to be the case, for, as has been pointed out by Hume and Gandevia (1957), this response also varies widely, and is least marked when the bronchial obstruction is at its worst.

Thus, the respiratory function tests which were done were of value in that they helped to eliminate patients with advanced emphysema, but otherwise they helped little in the prediction of the results of surgery.

Operation

The operation done was the same in each case. A short right thoracotomy was made, and the pleura was opened via the bed of the fifth rib. The amount of emphysema visible in the lung was noted. The pleura was opened over the vagus nerve, and the posterior pulmonary plexus was dissected from the azygos vein to the inferior pulmonary vein. All the branches passing to the lung were divided. These varied in number; there were usually three or four small branches and two big ones. The small contribution to the plexus arising from the dorsal ganglia of the sympathetic chain was divided as they joined the plexus from behind. The vagus was then isolated above the azygos vein, when a branch from it was usually found running behind the vein to the upper border of the right upper lobe bronchus; this was also divided.

The chest was closed with drainage. One patient developed an empyema after his operation; in the remainder the post-operative course was smooth.

Results

The assessment of the results of any form of treatment for asthma is notoriously difficult, and any method is apt to give relief for a short period. It was therefore decided not to attempt assessment until at least a year had passed since the operation.

Of the sixteen patients under review, twelve have been followed up for more than a year, eight for more than two years, and three for more than three years. One patient, a man aged 70 with a four months' history of status asthmaticus, died seven months after his operation with the disease still uncontrolled. The survivors were assessed under three headings: subjective changes, alteration in steroid dosage, and objective changes.

Subjective Changes

It was soon realised that although ideally the purpose of treatment is the complete relief of the disease, this was seldom achieved. Nevertheless, if it

could be shown that the frequency of severe attacks could be diminished, or if the severity of the attacks could be lessened and the loss of work reduced as a result, then the operation could be regarded as worth while. This was particularly true if the patient could return to steady work.

On this basis the patients were divided into three groups: those who were " much improved "; those who were " improved "; and those who were no better.

A patient was regarded as being " much improved " when either the attacks had been completely abolished (2 cases), or when they had been so reduced in severity or frequency that they no longer interfered with life or employment. Six of the patients were thought to fall into this group.

A patient was regarded as " improved " when the result was not as good as that described above, but was still good enough to allow him to lead a relatively normal life. In this group, although the attacks of asthma might be severe, they were now readily controlled by antispasmodics, and hospital admissions were uncommon. There were four patients placed in this group.

Two patients were " no better "; one of these improved for a while, but then deteriorated and has now had the left side operated upon as well as the right.

The results are shown in Table III. From this it can be seen that although

TABLE III

No.	*Sex*	*Work before operation*	*Work after operation*	*Result*
1	M.	Lost 3-4 months each year: 6 months in hospital before operation	One month's work lost since operation	" Much Improved."
2	M.	Unemployed for 4 years: many hospital admissions	Still out of work: no further admissions	" Much Improved."
3	M.	Unemployed for some years	Still unable to work	" No better."
4	F.	Very frequent hospital admissions	Twice in hospital for asthma in last two years	" Improved."
5	M.	No work for 4 months before operation	Returned to work 18 months after operation	" Much Improved."
6	M.	9 months off work in last year	One month lost since operation	" Much Improved."
7	M.	Only occasional work for 4 years	14 days' work lost since operation	" Much Improved."
8	M.	Retired: several hospital admissions	Died at seven months	
9	F.	Occasional hospital admissions	One admission since operation	" Improved."
10	F.	Repeated hospital admissions	Almost free of attacks after 18 months	" Improved."
11	M.	Unable to work for six months	Has lost no work since operation	" Much Improved."
12	F.	Unable to work for 10 months	Still unable to retain employment	" No better."
13	F.	Several hospital admissions	No admissions since operation	" Improved."

all except one of the patients had been receiving steroids before their operation, none of the men had been able to maintain steady employment. Five of the seven are now losing little or no time at work; of the other two who are still not working, one is virtually unemployable for other reasons.

The frequency of hospital admissions amongst the five women has been reduced. In one this was only achieved eighteen months after her operation, possibly because of alteration of her drugs at that time. One of the women who returned to work fourteen months after her operation has now relapsed.

Thus, in only three patients, one of whom died, was the operation completely unsuccessful, varying degrees of relief being claimed by all the other ten.

These results have by no means always been achieved immediately after surgery. Some of the patients had severe attacks while still in hospital and only improved over the next few months. (Reinof and Gay (1938) also made this observation in three of their cases.) Three patients did not achieve full benefit of the operation until more than a year after it. In some there was deterioration after initial improvement; in all except two this deterioration was readily controlled by restarting the steroids. Of the other two, one died at seven months; the other having gradually improved for more than a year deteriorated again and has now had bilateral pulmonary plexus resection.

Alteration in Steroid Dosage

All except four of the patients were receiving steroids at the time of their operation. Cortisone was given for forty-eight hours post-operatively, but after this an attempt was made to wean them from the steroids by the tenth day, as it was hoped that the operation would allow them to dispense with the drug altogether. It was found that few could do without the drug entirely, although one required none for a year and another did not start it again until twenty months after operation. It was, however, possible to reduce the dose in all those patients in whom the preoperative level was thought to have been too high, and no patient is now having more than 10 mg. of prednisone or its equivalent each day.

In some cases it was impossible to decide what part the operation played in the improvement, but in the majority it appeared that the combined effect of the drugs and surgery was greater than that of the drugs alone.

Thus, one of the aims of the operation, *i.e.*, the cessation of steroid therapy, was seldom achieved, but it was possible to reduce the dosage to an acceptable level in all cases.

Objective Changes

In each of the thirteen cases operated upon more than a year ago, respiratory function tests were repeated. The figures are given in Table IV. In some of the patients these tests have been done on several occasions since the operation and the figure given is the most recent one.

No consistent pattern emerges. The F.V.C. has risen in seven patients but has fallen in one; the F.E.V.I. has risen in eight but has fallen in two; the

TABLE IV

No.	*Change in F.V.C.*	*Change in F.E.V.1.*	*% Change in F.E.R.*	*Result*
1	1,300 c.c. up	600 c.c. up	2% up	"Much Improved."
2	I.S.Q.	400 c.c. up	14% up	"Much Improved."
3	300 c.c. up	600 c.c. up	20% up	"No better."
4	I.S.Q.	500 c.c. down	18% down	"Improved."
5	I.S.Q.	200 c.c. down	5% down	"Much Improved."
6	300 c.c. down	I.S.Q.	4% up	"Much Improved."
7	800 c.c. up	200 c.c. up	3% down	"Much Improved."
8	200 c.c. up	200 c.c. up	4% up	Died.
9	I.S.Q.	I.S.Q.	I.S.Q.	"Improved."
10	I.S.Q.	I.S.Q.	I.S.Q.	"Improved."
11	800 c.c. up	1,300 c.c. up	27% up	"Much Improved."
12	300 c.c. up	500 c.c. up	18% up	"No better."
13	400 c.c. up	600 c.c. up	25% up	"Improved."

F.E.R. has risen in eight but fallen in three. None of these figures could be correlated with the subjective findings.

Each of the three patients in whom the F.V.C. or the F.E.V.I. fell was "improved" or "much improved"; whereas there was no improvement in two of the patients in whom the F.E.R. rose by 18 per cent. and 20 per cent. respectively. These two patients who were "no better," and the one who died seven months after his operation, all had an increase both in the F.E.V.I. and in the F.V.C.

Thus it was not found possible to assess the results of the operation from objective evidence, but Table IV shows that in the majority of patients there was some rise in the F.V.C., the F.E.V.I. or the F.E.R.

Discussion

Sporadic attempts have been made to treat asthma by surgical means since Kummel first did so in 1923. Operations have been designed to interrupt the nerve supply to one or both lungs by division of the sympathetic, the parasympathetic, or both groups of fibres. Phillips and Scott (1929) analysed all the cases reported in the literature up to 1929. In all they found a description of 211 cases in which surgical treatment had been attempted. Of these, 48 per cent. were said to have been improved although the follow-up period was often short. The operative mortality was 1 per cent.

Reinhof and Gay (1938) advocated bilateral pulmonary plexus resection; Klassen and others (1950) divided both vagi below the recurrent laryngeal nerves; Blades and others (1950) performed either unilateral or bilateral pulmonary plexus resection; and Abbott and others (1950) performed sympathectomy in some cases and division of the vagal supply to the lungs in others. All these authors claimed a proportion of successes (Table V).

The introduction of the steroids for the treatment of asthma was an important advance. This form of treatment has been shown to give reasonably

consistent results, and can be carried out for long periods (Somner and others, 1960; Phear and others, 1960). The reported results of operative treatment have been less consistent, but hitherto no series has been published in which the two methods have been combined.

In previous series operations have often been carried out in patients with irreversible lung damage due to bronchitis, emphysema, bronchiectasis, or bullous cysts. It may well be that the inconsistency of the results was due to this fact alone, and all such cases have been excluded from this series.

In 1957 Szokodi revived interest in the surgical approach to the disease when he reported the results of bilateral pulmonary plexus resection in nineteen patients. More recently Overholt (1959) has described his experiences with a further 43 cases, 15 of which had pulmonary plexus resection. Although neither of these authors confined the operation to patients suffering from pure asthma, both claimed considerable improvement in more than half their cases.

TABLE V

Author	*No.*	*Operation*	*Op. Mort.*	*Late Mort.*	*M.I.*	*I.*	*P. or W.*
Reinhof	10	Bilateral plexectomy	—	1	4	4	1
Klassen	3	Bilateral vagotomy	1	—	1	—	1
Blades	38	Bilateral and unilateral vagotomy	1	6	14	8	9
Abbott	18	Plexectomy	4	—	5	4	5
Clarke	6	Bilateral plexectomy	—	1	—	—	5
Szokodi	19	Bilateral plexectomy	1	—	10	7	1
Overholt	15	Bilateral and unilateral plexectomy	1	3	7	3	2
Belcher	13	Right plexectomy	—	1	6	4	2
Totals	122		8 (6·5%)	12 (10%)	47 (39%)	30 (25%)	26 (21%)

Reinhof and Gay (1938) stressed the necessity of operation on both sides, and Abbott and others (1950) and Overholt (1959) thought it essential to remove " trigger areas " of diseased lungs. The operations in this series were confined to the right side, and in no case was any lung tissue removed. The results reported when only one side was operated upon appeared to be comparable with those where both plexuses were resected, and therefore only one side was done in the first place. The short-term follow-up suggested that this might be sufficient, and so far it has been thought necessary to operate on the second side in only one patient.

Although Blades and others (1950) operated upon the left side when doing a unilateral operation because the nerve supply to that lung appeared to be

richer, the right side was chosen in this series as it was thought that the risk of damage to the recurrent laryngeal nerve was less on this side.

Table V shows the results of bilateral and unilateral pulmonary plexus resection reported in the literature since 1929. It will be seen that the operative mortality was 6·5 per cent. but that the late mortality was higher, most patients dying with uncontrolled asthma. On the other hand, of the survivors, 39 per cent. were considered to be " much improved " and only 21 per cent. were no better or worse. The proportions in each series were roughly the same.

The results in the series reported here tend to confirm the opinion of previous authors that there is a limited place for surgery in the treatment of asthma. It is therefore suggested that if a patient has pure asthma with little or no lung disease; if steroid therapy has led to complications or has become ineffective; or if the dosage required to control the disease has become too high, then if the patient is severely disabled, pulmonary plexus resection should be considered.

If the operation is confined to pure asthmatics, the results appear to be sufficiently consistent to justify this policy, and it may well be that the more rigidly the patients suffering from emphysema are excluded, the more consistent the results will become.

Summary

1. Right pulmonary plexus resection has been carried out in sixteen patients for the treatment of asthma.

2. The results of this procedure have been assessed in the thirteen patients who had this operation more than a year ago.

3. All except one patient had had steroid therapy before operation, and in fourteen this was continued or restarted after operation.

4. One patient died seven months after his operation; of the remaining twelve, six are " much improved," four are " improved," and two are " no better."

5. The results of surgery seem to justify its consideration in patients severely disabled despite steroid therapy.

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CENTRIFUGAL METASTASIS IN LUNG CANCER

By W. I. B. Onuigbo

Pathology Department, University and Western Infirmary, Glasgow

In a recent Harveian Oration, Melville Arnott (1955) commented on the need to watch for the unexpected and the anomalous as these may imply imperfections in our current concepts. The present paper draws attention to, and offers an explanation for, one anomaly in our concept of metastasis in lung cancer.

Three decades ago, Fried (1931) wrote that the frequency of metastasis in lung cancer " diminishes with the distance from the central axis of the body." More recently, Fried (1948) explained: " In only rare instances were metastases found in the abdominal viscera below the region of the kidney "; or, as Maher and Staderman (1940) put it, carcinomatous spread from the lung was " most often restricted to the hilar areas, the mediastinum, the liver, the adrenals and the kidneys." It is not surprising, therefore, that Karsh (1951) was struck by the relative infrequency of ovarian metastases in lung cancer. Indeed, Enticknap (1952), who believed that lung cancer spreads more widely than almost any other tumour, was constrained by the scarcity of ovarian metastases to say that this was " a remarkable example of the difficulty of generalizing about tumour behaviour."

These observations suggest that the more distant an organ is from the primary pulmonary growth, the less often it exhibits metastases. This is surprising for tumour cells originating in the lung have only to penetrate the pulmonary veins to be carried to the left side of the heart and aorta and so to be dispersed to organs far and near.

Two questions arise for consideration. Does analysis of ascertainable facts support the view that lung cancer spreads centrifugally to the viscera? If this is confirmed, how can it be accounted for? In a preliminary study of a limited number of cases (Onuigbo, 1957), I touched briefly on these questions. It is the purpose of the present paper to examine the problem in detail.

Investigation

Theoretical considerations lead to the view that the two lobes of the liver, the two adrenals, and the two kidneys are so located that each of the three organs has a fair chance of receiving tumour cells not only when the metastasising tumour originates in the right or left lung, but also when these cells are blood- or lymph-borne. The three organs can be used in comparing the frequency of metastases.

Note was made of the presence of macroscopic metastases in the liver, adrenal and kidney in a survey of the necropsy records of 6,000 cases of lung

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cancer in Medical Schools throughout Britain. Another series of 6,000 cases of lung cancer was collected from the literature.

Three cases showing the state of the para-aortic lymph nodes in the abdomen of patients dying with lung cancer are illustrated (Figs. 1-3). These cases have been selected from those collected in a collateral study in which the topographical distribution of lymph node metastases is being investigated by dissection of fixed tissues obtained *en bloc* at post-mortem.

Results

Table I shows that in the Medical School series the order of metastasis was liver, 2,450; adrenal, 2,009; and kidney, 1,003. Table II reveals a closely comparable order: liver, 2,391; adrenal, 1,897; and kidney, 1,172.

Fig. 1 illustrates the appearance of the para-aortic abdominal lymph nodes when macroscopic metastases are not present in patients dying with lung cancer. Figs. 2 and 3, on the other hand, illustrate the typical appearance when many nodes are macroscopically invaded. It is seen that metastasis is centrifugal,

TABLE I.—THE DISTRIBUTION OF METASTASES IN 6,000 CASES OF LUNG CANCER COLLECTED FROM THE MEDICAL SCHOOLS

Medical School	*Total*	*Liver*	*Adrenal*	*Kidney*
Glasgow—Western Infirmary	352	146	142	59
Royal Infirmary	359	161	113	63
Edinburgh	355	161	104	55
Aberdeen	200	87	82	39
Dundee	100	37	31	19
London—Hammersmith Hospital	419	180	151	67
St. Mary's „	400	164	138	92
The London „	400	139	139	62
St. George's „	266	100	87	35
Guy's „	246	108	83	50
Middlesex „	200	87	66	25
Univ. Coll. „	200	90	68	45
St. Thomas's „	133	75	58	37
Westminster „	130	61	46	25
King's Coll. „	119	39	32	16
Charing Cross „	117	51	41	22
St. Barth's „	100	51	46	22
Royal Free „	100	45	37	17
Leeds	548	183	186	75
Oxford	300	119	72	34
Manchester	200	70	58	34
Newcastle	172	74	59	23
Cambridge	100	46	28	13
Birmingham	100	30	14	8
Bristol	100	48	38	25
Cardiff	100	28	25	9
Sheffield	100	38	38	20
Liverpool	84	32	27	12
Totals	6,000	2,450	2,009	1,003

TABLE II.—THE DISTRIBUTION OF METASTASES IN 6,000 CASES OF LUNG CANCER COLLECTED FROM THE LITERATURE

Authors	*Total*	*Liver*	*Adrenal*	*Kidney*
Farber (1954)	1,070	479	428	286
Bryson (1949)	866	307	206	107
Galluzi and Payne (1955)	741	291	247	114
Halpert *et al.* (1960)	363	161	139	74
Senoo (1956)	336	133	95	93
Cameron (1954)	302	114	115	42
Howell and Piggot (1957)	300	103	77	35
Walther (1948)	286	117	42	56
Budinger (1958)	250	105	83	48
Enticknap (1952)	196	83	59	35
Tenzel (1941)	192	74	69	35
Abrams *et al.* (1950)	160	64	57	36
Shik (1946-47)	138	50	38	38
Gibson (1952)	120	34	32	17
Wegelin (1942)	117	54	24	26
Strang (1949)	100	38	26	15
Koletsky (1938)	100	40	38	21
Stein and Joslin (1938)	100	41	31	25
Samson (1935)	100	35	21	25
Jaffe (1934)	100	36	42	28
Henkin (1947)	36	17	16	12
Willis (1941)	27	15	12	4
Totals	6,000	2,391	1,897	1,172

the proximal nodes being earlier and more grossly involved. Thus, both lymph node metastases and visceral metastases in the abdomen are centrifugal.

Discussion

The length of time the primary tumour has been present is an important factor which determines the occurrence of metastasis (Haddow, 1938). Patterns of metastasis also unfold with time. Thus, propagation occurs progressively to more and more distant lymph nodes. This characteristic centrifugal distribution was known to Paget (1870), is readily observed in cases of lung cancer (Boyd, 1932; Spencer, 1954), and has been confirmed by diverse experiments, *e.g.* with radioactive colloids (Walker, 1950), vital dyes (Weinberg, 1951), tubercle bacilli (Russell, 1905), and tumour cells (Pearce and Brown, 1923).

Centrifugal metastasis may, as in the case of the abdominal nodes, be in a retrograde direction *i.e.* contrary to the accepted course of lymph flow. Do the tumour cells in their retrograde wanderings discriminate between one lymph pathway and another? In particular, are these cells capable of conducting themselves along channels leading to the nodes while adroitly avoiding similar channels leading to the viscera? Since both the viscera and the lymph nodes themselves drain into lymph nodes, when metastasis occurs in the reverse direction, both the viscera and the lymph nodes would be susceptible to attack via the lymphatics. The current teaching that lymph spreads cancer to the node while blood carries it to an organ requires revision.

FIG. 1.—Showing state of para-aortic abdominal lymph nodes when they are not metastasized (*Glasgow Western Infirmary Case B2600*). The adrenal glands are left *in situ*.

FIG. 2.—Showing state of para-aortic abdominal lymph nodes which are metastasized (*Glasgow Western Infirmary Case B2553*). The adrenal glands are left *in situ*.

FIG. 3.—Showing state of the lympth nodes at a more advanced stage (*Glasgow Western Infirmary Case B2607*). The adrenal glands are left *in situ*.

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A possible objection may be anticipated. Willis (1952) says that " discrete " deposits of tumour within distant organs are almost always blood-borne. Is discreteness of a visceral deposit a valid argument for rejecting the possibility of its being lymph-borne? We have historical references to the fact that discrete deposits occur along the lymphatics (Andral, 1831; Wilks and Moxon, 1875); we have experimental confirmations (Pearce and Brown, 1923; Zeidman, 1959); and we have autopsy observations (Boyd, 1930; Cappell, 1958). Besides, discrete deposits are readily demonstrable within the lymph nodes both macroscopically and microscopically. Even Sampson Handley (1955), who initiated the permeation theory of lymphatic spread, was aware that among " the peculiar marks of a lymphatic disease " is included the fact that " the lesions are nodular," as well as that " nodular deposits may appear along the course of the trunk lymphatic vessels." Willis (1960) himself, when controverting the permeation theory, wrote: " Even in advanced cases with multiple glands (lymph nodes) affected, it is likely that embolism from gland to gland is largely responsible, for the affected glands may at first be discrete and unconnected." All are therefore agreed that discrete deposits occur in lymphogenous dissemination. Certainly, such deposits are not incompatible with lymph-borne metastasis.

In lung cancer, according to Boyd (1930), spread through the pulmonary parenchyma " is mainly lymphatic in type, and by this means multiple nodules may be formed." The evidence now presented calls for the recognition of the fact that similar nodular deposits in the parenchyma of distant viscera are compatible with, and explicable on, lymphogenous dissemination.

Summary

The literature contains references to the centrifugal nature of the topographical distribution of visceral metastases in lung cancer. Since the current theory is that visceral metastases are hæmatogenous, this pattern is unexpected.

6,000 cases of lung cancer were obtained from Medical Schools throughout Britain. Another 6,000 cases were collected from the literature. In both series centrifugal metastasis was apparent, the percentage frequency of metastases being liver, 40·8 and 39·9; adrenal, 33·5 and 31·6; and kidney, 16·7 and 19·5 respectively. Evidence is presented that in lung cancer the abdominal lymph nodes are metastasised centrifugally. It is suggested that lymphogenous metastasis is compatible with, and accounts for, discrete secondary deposits not only in the lymph nodes but also in the viscera within the abdomen.

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A TRIAL OF ETHIONAMIDE

By G. W. Allan, A. W. Lees and G. B. S. Roberts

From Ruchill Hospital, Glasgow

Ethionamide (2-ethylthioisonicotinamide; "1314"; Trescatyl), a new oral, anti-tuberculous drug, has shown promise in preliminary trials in this country (Somner *et al.*, 1959; Riddell *et al.*, 1960). We report here results in 78 patients, 54 of whom have completed at least three months' therapy. All of these patients had chronic disease and in most, therapy with standard drugs was ineffective because of bacterial resistance. In the remainder therapy with standard drugs was not feasible for other reasons such as drug toxicity.

Methods

Patients were given 1 g. ethionamide daily. Examination of the urine was carried out daily; direct microscopic examination of respiratory secretions weekly; blood urea estimation, liver function tests and blood count fortnightly; and chest X-ray and culture of respiratory secretions monthly.

Specimens of sputum were concentrated by Petroff's method and cultured on Löwenstein Jensen media. Sensitivity tests against ethionamide were carried out by incorporating the drug in Löwenstein Jensen medium. Owing to poor solubility it proved necessary to dissolve it in hot distilled water which was then incorporated into the medium. Concentrations of 5, 10, 25, 50 and 100 micrograms/ml. were used. All batches of media were tested against strain H37 RV and against known resistant strains.

Sensitivity tests against a range of antibiotics were performed using commercially prepared media in which the following strengths of antibiotic were incorporated:

	Micrograms
PAS	2 and 100
streptomycin	3 and 30
isoniazid	5 and 50
cycloserine ..	20, 40, 60 and 80

Toxic Reactions

Therapy had to be stopped in 32 of the 78 patients because of toxic reactions, in 15 instances within fourteen days, in 9 between fourteen days and three months, and in 8 after three months.

Toxic effects necessitating cessation of therapy within fourteen days were nausea, vomiting, metallic taste in the mouth, anorexia and, occasionally, headache. Persisting anorexia was the main toxic effect between fourteen days and three months. Toxic effects necessitating cessation of therapy after three months (in 8 patients) were mental disturbance (in 3), swelling of the face (in 2), anorexia (in 2), and skin sensitisation (in 1). In 2 of these 8 patients

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referred to, toxic effects were first noted as long as eight months after the start of treatment, and consisted of mental disturbance in 1 case and swelling of the face in the other. Evidence of toxic effects on the liver, kidneys, or hæmopoietic system was not observed.

Bacteriological Results

In all but 5 of the 54 cases completing three months' therapy ethionamide was accompanied by a drug to which the organisms were sensitive (in the case of pyrazinamide it was presumed that the organisms were sensitive as the drug had not previously been used). PAS 15 g. daily was given in 35 cases, pyrazinamide 1·75 g. daily in 6 cases, isoniazid 400 mg. daily in 4 cases, streptomycin 1 g. daily in 3 cases and cycloserine 1·5 g. daily in 1 case.

If conversion is defined as a negative culture and negative weekly direct examinations during the preceding month, then at three months 15 (43 per cent.) of the 35 ethionamide/PAS cases, 2 (33 per cent.) of the 6 ethionamide/pyrazinamide cases, 2 (50 per cent.) of the 4 ethionamide/isoniazid cases and 1 (33 per cent.) of the 3 ethionamide/streptomycin cases had converted. (That is 41 per cent. of the 48 cases treated with ethioniamide plus another drug.) None of the 5 cases on ethionamide alone had converted at that time, nor had the case on ethionamide/cycloserine.

Eleven of the 35 ethionamide/PAS cases have now been followed for six months: 7 of the 15 cases which converted and 4 of the 20 which did not convert; 2 of the 7 that converted have become positive, and none of the 4 unconverted at three months have converted at six months.

Initial sensitivity tests were available in 7 of the 15 ethionamide/PAS patients who converted at three months; 3 of the 7 were completely sensitive to ethionamide in all concentrations and the others showed varying degrees of resistance. Initial sensitivities were available for 17 of the 20 ethionamide/PAS patients who did not convert at three months. Six were completely sensitive, and 11 showed varying degrees of resistance. Five of the 6 patients initially sensitive had become markedly resistant to ethionamide by three months, and three of these 5 patients had also become resistant to PAS. All the 11 patients with some initial resistance had become markedly resistant to ethionamide, and 6 of these 11 patients had become resistant to PAS. Initial sensitivity tests to ethionamide were available in both the ethionamide/pyrazinamide patients who converted at three months: neither was completely sensitive. Initial sensitivities to ethionamide were available in 3 of the 4 ethionamide/pyrazinamide patients who did not convert: only one of the 3 was completely sensitive; and at three months all were markedly resistant to ethionamide.

One of the 2 ethionamide/isoniazid patients who converted at three months had organisms initially completely sensitive to ethionamide. One of the 2 ethionamide/isoniazid patients who did not convert at three months had organisms initially sensitive to ethionamide; by three months the organisms had become resistant to ethionamide, but were still sensitive to isoniazid. The organisms of the ethionamide/streptomycin patient who converted at three months were not initially completely sensitive to ethionamide nor were the

organisms of the 2 who did not convert, but at three months the organisms of these 2 patients were still sensitive to streptomycin.

The organisms of the ethionamide/cycloserine patient were not initially completely sensitive to ethionamide and conversion was not achieved; at three months the organisms were still sensitive to cycloserine, and no change in the sensitivity pattern to ethionamide had occurred.

Initial sensitivity tests were available in 4 of the 5 patients treated with ethionamide alone. Only in 1 were the organisms completely sensitive, and in all they had become markedly resistant at three months.

Whether or not isoniazid was given to patients in the series, isoniazid sensitivities were obtained; there was no evidence of cross-resistance between isoniazid and ethionamide.

Radiological Progress

Potential radiological improvement was limited in the majority of cases by the chronic and intractable nature of the disease, and improvement was assessed as good, fair or slight, bearing this in mind. Films were compared without the reader knowing the sequence in which they were taken; therefore, although classification of the degree of improvement is arbitrary the results should give a reliable indication of the proportion in which some improvement took place.

Of the 35 patients completing three months' therapy with ethionamide and PAS 19 (54 per cent.) improved and 16 (46 per cent.) did not. The degree of improvement was assessed as good in 8 (23 per cent.), fair in 5 (14 per cent.) and slight in 6 (17 per cent.). Initially 54 cavities were noted in this group of patients; by three months 6 had closed, 14 had become smaller and 34 were unaltered.

Of 6 patients treated with ethionamide/pyrazinamide, 3 improved. The degree of improvement was assessed as good in 1, fair in 1 and slight in 1. There were 5 cavities initially in this group; none closed, 1 became smaller and 4 were unchanged. Of 4 patients treated with ethionamide/isoniazid 3 improved. The degree of improvement was assessed as good in 2 and slight in 1. There were 5 cavities initially in this group; 1 cavity closed, 2 cavities became smaller and 2 were unchanged. Of 3 patients treated with ethionamide/streptomycin, 2 improved. There were 4 cavities initially in this group; 1 became smaller and 3 remained unchanged.

The patient treated with ethionamide/cycloserine improved. The degree of improvement was assessed as good. This patient had 2 cavities; 1 closed and 1 became smaller. Of the 5 patients treated with ethionamide alone, 2 improved. The degree of improvement was assessed as good in 1 and fair in 1. There were 6 cavities initially in this group; 2 became smaller and 4 were unchanged.

Discussion

Bearing in mind the chronic type of disease for which ethionamide was given in this trial, the results indicate that the drug has considerable anti-tuberculous

activity: with PAS as a companion drug radiological improvement was noted in half the patients after three months' therapy and in a few cavity closure was achieved. Nevertheless ethionamide has serious limitations. In the dosage employed (1 g. per day), 41 per cent. of patients were unable to tolerate the drug, often at an early stage. Moreover, it appears that unless conversion of sputum is obtained in the early weeks of therapy emergence of ethionamide resistance is the general rule whether the drug is given alone or accompanied by PAS. As might be expected, when resistance develops to ethionamide, resistance to the companion drug is also apt to develop as was seen in the case of PAS in this series. The number of instances in which ethionamide was given along with a drug other than PAS is too small to draw definite conclusions from the results, but the trends were the same as when ethionamide was used with PAS.

It may be that the results of this trial do not fully reflect the effectiveness of ethionamide, as at first patients were treated with coated tablets and it has been found that absorption is more complete with uncoated tablets. Yet the fact that a considerable proportion of patients receiving coated tablets had difficulty in tolerating the drug suggests that the blood levels achieved were as high as was practicable. However, a higher rate of bacteriological conversion was achieved in patients receiving uncoated tablets than in patients receiving coated tablets. Nevertheless the degree of radiological improvement was no better in patients receiving uncoated tablets and there was the same tendency towards emerging resistance if bacteriological conversion was not speedily attained.

In the present trial a high proportion of patients was unable to tolerate 1 g. of ethionamide per day, yet the tendency to emerging drug resistance suggests that it would be unwise to employ a lower dosage at least when given with PAS. The impressive improvement noted in certain cases indicates that the drug may prove of considerable value.

Summary

Seventy-eight patients with chronic disease were treated with ethionamide (1 g. per day), in 73 instances in combination with a drug to which the bacteria were still sensitive. In the remaining 5 instances no effective companion drug was available. Thirty-two of these patients were sooner or later unable to tolerate the drug. Results at three months have been analysed for 35 patients on ethionamide/PAS; 6 on ethionamide/pyrazinamide; 5 on ethionamide alone; 4 on ethionamide/isoniazid; 3 on ethionamide/streptomycin and 1 on ethionamide/cycloserine. In about half the cases some degree of initial ethionamide resistance was noted although patients had not previously received the drug. Drug resistance invariably rapidly developed or increased in patients treated with ethionamide alone, and resistance tended to develop or increase in a proportion of patients in whom ethionamide was accompanied by PAS or other drugs to which the organisms were initially sensitive. The value of the drug when combined with PAS appears to be limited by the

inability of many patients to tolerate it in a dosage high enough to prevent the emergence of resistant organisms. Experience with ethionamide combined with other drugs was too small to permit firm conclusions to be drawn. The impressive radiological and bacteriological results obtained with ethionamide and PAS in a considerable proportion of patients with intractable disease suggests that ethionamide may prove a useful therapeutic agent.

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THE CLINICAL PATTERN OF RESISTANCE IN PULMONARY TUBERCULOSIS

By P. O. Leggat
Newcastle Chest Clinic

The emergence of resistant organisms has always been viewed with alarm by physicians treating cases of pulmonary tuberculosis. This paper is based on the study of forty-nine cases of pulmonary tuberculosis attending a Chest Clinic, who developed resistance to one or more of the standard drugs while undergoing treatment. It covers the period January 1951 to October 1960.

The group contained thirty-three men and sixteen women. Thirty-six of the cases were over the age of forty years (Table I). Thirteen of them are now dead, the majority due to progressive tuberculosis, but one died from carcinoma of the lung, another from carcinoma of the stomach, and a third from chronic myeloid leukæmia.

Table I.—Age (Years)

20-29	*30-39*	*40-49*	*50-59*	*60+*
9	4	15	12	9

Resistance tests were carried out with Löwenstein Jensen medium containing the following concentrations of anti-tuberculous drugs: isoniazid 0·2 μg. per ml., PAS 2·0 μg. per ml., and streptomycin 3·0 μg. per ml. The inoculation of the Löwenstein Jensen slopes was carried out by means of a swab. In forty-six instances the resistance was to isoniazid, while in twenty-six streptomycin was the culprit, followed by PAS in twenty.

The majority of the patients had an adequate total amount of therapy as forty-three of them had twelve or more months of treatment (Table II). Only six patients had less than a total of twelve months of therapy and three of these died before completing treatment. In many cases the therapy had been of a very intermittent character and had often been associated with repeated relapses.

Table II.—Duration of Therapy

< 12 months	*12 to 24 months*	*> 24 months*
6	26	17

By the application of chemotherapy and the use of surgery in two cases, conversion of sputum on culture was obtained in sixteen out of the thirty-six

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cases still alive. Of the twenty patients with positive sputum, four are still earning.

Multiple resistance was associated with failure of conversion as there were 12 (60 per cent.) cases in the " live positive " group and only 8 (50 per cent.) in the " live negative " group, which demonstrated resistance to more than one of the standard drugs. In the " live positive " group, the main factors associated with the failure of conversion in twenty cases appear to be: age (as eighteen were over the age of forty years), extensive disease (as in sixteen it occupied more than three zones), and the development of multiple resistance which occurred in twelve cases. In only four was the patient totally uncooperative (Table III).

TABLE III.—FACTORS ASSOCIATED WITH CONVERSION FAILURE

> 40 years	*Unco-operative*	*Disease three zones*	*Multiple resistance*
18	4	16	12

Discussion

Prevention is quite obviously better than cure in this particular problem. On reviewing the therapy given to the forty-nine patients it appeared that bad therapy, *i.e.* single drugs, unorthodox combined therapy or calcium PAS combined therapy, was only used in eleven instances before the development of resistance. One is therefore forced to the conclusion that the emergence of resistance, and in particular isoniazid resistance, is due to failure on the patient's part. The opportunity was available as thirty-two of the forty-six cases with isoniazid resistance had one or more courses of PAS combined with isoniazid, and seventeen of the twenty-six cases resistant to streptomycin had one or more courses of PAS with streptomycin. It is known that the rate of failure to take PAS, particularly at home, is high. (Simpson, 1956; Dixon *et al.*, 1957; Wynn-Williams *et al.*, 1958; *Tubercle*, 1959.) In these series PAS with isoniazid was frequently used for domiciliary therapy. Except for the inconvenience, there are good grounds for replacing domiciliary PAS with streptomycin, at least in the initial therapy, as some of the patients regularly take less than the recommended number of cachets (Dixon *et al.*, 1957; Leggat, 1957). Qualitative tests for PAS in the urine will be positive although the serum levels for the drug may be below the optimum.

Seventeen of the cases continued to improve and finally became negative on culture, even when orthodox therapy was continued. This included six in the " living negative " group who were resistant to two out of the three standard drugs. If resistance had developed to only one of the drugs, then that drug was discontinued. This suggests that a quantitative bacterial factor may be as important as a qualitative, in that bacterial populations are not homogeneous, numerically or in degree, in regard to resistance.

With the development of resistance to all three standard drugs, the position is much more serious. Four cases of this type were found in the " living positive " group. The only one that occurred in the " living negative " group was a case of primary resistance, and she responded to cycloserine, viomycin and oxytetracycline (Terramycin). In the remaining three " negative living " cases, one finally converted with cycloserine, oxytetracycline (Terramycin) and viomycin; another with streptomycin, cycloserine and ethionamide; and one with viomycin, PAS and cycloserine.

The number of cases coming to surgery was disappointingly small; this was because of the twenty who were still alive and positive, most were old and had very extensive disease.

In the case of the four patients who completely failed to co-operate, two were well advanced in years, aged seventy-three years and eighty-eight years, and therefore had a very circumscribed social field for potential infection due to poor physical condition limiting their movements. Of the other two, one is working as an enquiry agent and the other is dead. Such cases raise the question of compulsory admission (Flynn, 1960; Davis *et al.*, 1960). Before taking such a step it is only right that there should be a reasonable possibility of the sputum being converted. Should such people be allowed to earn their living, they should do so only under very carefully approved conditions.

In this particular series, the middle-aged men with extensive disease were the most likely candidates for the development of resistance, about half of the resistant cases were converted by chemotherapy, and the majority of the remainder were unsuitable for surgery on account of age usually in conjunction with extensive disease.

In spite of the recommendation by the supervising physician, of adequate chemotherapy, there is a steady yearly increment of resistant cases, due to failure of the patient to take his drugs (Leggat, 1957; Dixon *et al.*, 1959).

These results indicate the necessity for continuous long-term chemotherapy for at least eighteen months and, in cases which take a long time to convert to a negative sputum, this period should be considerably increased. They also indicate the importance of testing the sputum regularly for sensitivity to the drugs, in order to maintain an adequate cover with effective drugs, and lastly, the importance of adequate supervision in the positive cases to prevent the spread of disease, especially when the patient has resistant bacteria, because of the subsequent difficulty in controlling disease caused by such bacteria.

Summary

Forty-nine cases of pulmonary tuberculosis resistant to one or more of the standard drugs are reviewed.

Ten of the patients died from the disease.

Forty-six of the cases were resistant to isoniazid; twenty-six to streptomycin and twenty to PAS. Twenty of the thirty-six living cases remained positive due to extensive disease, multiple resistance, advanced years and failure to co-operate.

The development of resistance was due to bad therapy in eleven cases.

Prolonged intermittent therapy with relatively short courses of chemotherapy dictated by relapse was an aggravating factor. In the majority of instances it appeared that the most likely cause was failure of the patient to take PAS regularly or in adequate dosage.

Surgery was feasible only for the minority.

The sputum of sixteen of the live cases was converted by medical treatment.

I am indebted to Dr. C. Verity and Dr. L. W. Carstairs for allowing me access to the case records of their patients, and to Dr. J. H. Hale and Dr. A. E. Wright for carrying out the resistance tests.

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Brit. J. Dis. Chest (1961) 55, 100.

PULMONARY TUBERCULOSIS FOLLOWING TREATMENT WITH CORTICOSTEROIDS

REPORT ON SIX CASES

By C. Stephanopoulos

Athens University Phthisiological Clinic

Cases of pulmonary tuberculosis, or flare-ups of latent foci, occurring in patients previously free of tuberculosis and submitted to treatment with corticosteroids, have been reported by King *et al.* (1951), Kleinschmid and Johnston (1951), Fred *et al.* (1951), Harris-Jones and Pein (1952), Davidson *et al.* (1953), Hill and Kirshbaum (1956), and Mackinnon (1959).

The widespread therapeutic use of corticosteroids at the present time, taken in conjunction with the effects that cortisone is known to have on tuberculous foci, warrants a thorough study of similar cases. During the last three years we have observed five such cases, four at our clinic and the fifth at the Armed Forces General Hospital. (The last case was placed at our disposal by the Consultant Physician of the Medical Clinic, Dr. Samaras.) In all five treatment with corticosteroids was instituted for diseases other than tuberculosis. In each roentgenological investigation before the corticosteroid therapy was negative for pulmonary tuberculosis.

Case 1. This was a 34-year-old woman from Cyprus who had no previous history of tuberculous infection. She had developed fever up to 39°C., arthralgia and œdema of the extremities. Antibiotics were given with no result. A chest roentgenogram was normal. In May 1956 treatment with D-Cortril was instituted. The initial daily dose was 30 mg. which was gradually reduced to 15 mg. by November 1956. The symptoms regressed but discontinuation of the treatment led to their reappearance.

In November 1957 the patient was admitted to the 2nd University Medical Clinic in Athens. Disseminated lupus erythematosus was diagnosed and a chest roentgenogram revealed a moderately advanced pulmonary tuberculosis with cavitation in the right lung (Fig. 1). Tubercle bacilli were present in the sputum.

In December 1957 the patient was admitted to our clinic with fever, intense arthralgia, œdema of the extremities and considerable loss of weight. She was immediately submitted to bacteriostatic treatment with streptomycin 1 g. and INH 300 mg. daily. The D-Cortril therapy was resumed at 15 mg. daily. This regimen was maintained for four months. A chest roentgenogram then revealed considerable clearing of the tuberculous lesions. The sputum was negative for tubercle bacilli. However, the disseminated lupus erythematosis became worse and she died in December 1958.

Case 2. A 34-year-old woman, with no previous history of tuberculosis, developed continuous fever between 38°C. and 39°C., with vomiting and

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arthralgia. Antibiotics and antirheumatic drugs were given with no result. In April 1958 the patient was admitted to the Evangelismos Hospital with a diagnosis of lymphogranuloma of the spleen. A chest roentgenogram revealed calcified hilar nodes on the right side.

The patient was submitted to radiation therapy of the spleen. Prednisolone 30 mg. was given daily but gradually reduced to a daily dose of 15 mg. After four months' treatment there was marked general improvement in her condition. She was advised to continue the prednisolone treatment at a daily dose level of 10 mg. for another month.

Seven months later a chest roentgenogram disclosed a bilateral, moderately advanced cavitary pulmonary tuberculosis (Fig. 2). The sputum was positive for tubercle bacilli. The prednisolone treatment was discontinued and treatment with streptomycin 1 g. and INH 500 mg. daily was instituted.

Twenty days after the patient's admission low-grade fever up to 37·8°C. and vomiting occurred. This was relieved by giving soludacorten 25 mg. daily. Whenever an attempt was made to discontinue the treatment there was a recurrence of the symptoms. The combined treatment with streptomycin, INH and soludacorten was therefore continued. One month later soludacorten was replaced by prednisolone 20 mg. daily, a dose that was gradually reduced to 10 mg. daily. Complete recession of the symptoms was achieved and there was a marked roentgenographic clearing of the lesions.

In November 1959 the streptomycin treatment was discontinued, and the prednisolone dose was reduced to 5 mg. daily. In January 1960 it was discontinued altogether. On March 1, 1960, the patient was discharged in a satisfactory general condition and free from symptoms. The sputum was negative for tubercle bacilli.

Case 3. A 35-year-old man, with no past history of tuberculosis, developed in the winter of 1959 a persistent dry cough and dyspnœa. In May 1959 a chest roentgenogram revealed a bilateral enlargement of the hilar nodes with juxtahilar infiltrate on the left lung and foci bilaterally (Fig. 3). The sputum was found to be negative for *Mycobacterium tuberculosis*. In July 1959 his general condition was satisfactory and gastric lavages for tubercle bacilli were negative. The sedimentation rate was 12/30 mm. The Mantoux reaction at 1 : 1,000 of old tuberculin was negative.

A diagnosis of sarcoidosis was made and treatment with prednisolone was instituted at 30 mg. for one week, then 20 mg. for 10 days, 15 mg. for 20 days and 10 mg. daily to complete a period of treatment lasting three months. There was marked clinical response, and both cough and dyspnœa were reduced. A chest roentgenogram (Fig. 4) revealed complete clearing of the parenchymal lesions, together with a marked recession of the hilar nodes. The patient was discharged in October 1959. The prednisolone treatment was continued in a dosage of 5 mg. daily.

Seven months later the patient was complaining of cough, fatigue and loss of appetite. A chest roentgenogram revealed a subclavicular infiltrate in the right lung (Fig. 5). Examination of the sputum and of gastric lavage specimens for *Mycobacterium tuberculosis* showed these to be negative. The Mantoux tuberculin reaction was intensely positive at 1 : 1,000. Treatment with streptomycin 1 g. and INH 300 mg. daily was immediately instituted. This led to marked clinical and roentgenographic improvement.

CASE 4. A 57-year-old man, with no previous history of tuberculosis, had been hospitalised at various institutions for loss of weight, marked asthenia, pains and œdemas of the lower limbs and low-grade fever up to 37·8°C.

In March 1959 nodular periarteritis was diagnosed after biopsy in the region of the right leg. Soludacorten 50 mg. was given daily for one month, resulting in marked clinical response. The treatment was discontinued because of uræmia. The general condition remained improved until December 1958 when he deteriorated. The soludacorten treatment, at 50 mg. daily, was resumed for fifteen days. One month later the same daily dose was again given for fifteen days, but was then discontinued because of an increase in the blood urea. In April 1960 he developed pains in the right hemithorax, accompanied by mucopurulent sputum and fever up to 38°C.

A chest roentgenogram showed a right pleural effusion and bilateral disseminated bronchopneumonic foci (Fig. 6). The sputum was positive for tubercle bacilli. A chest roentgenogram before treatment with corticosteriods showed no tuberculous lesions. The patient was given streptomycin 1 g. and INH 300 mg. daily. There was marked clinical response and roentgenographic clearing. The sputum became negative.

CASE 5. In February 1960 a 68-year-old man, with no past history of tuberculosis, developed very painful lumbago. He was given daily injections of soludacorten 50 mg. for one month. On the fortieth day of treatment he developed high fever. A chest roentgenogram was normal. The sedimentation rate was 50/83 mm. Examination of the sputum for tubercle bacilli was negative. He had enlargement of both spleen and liver. Broad spectrum antibiotics were given but there was no improvement.

In May 1960 a chest roentgenogram revealed a dense bilateral miliary spread (Fig. 7). The sputum continued to be negative and the Mantoux old tuberculin reaction was also negative at 1 : 1,000. Treatment with streptomycin 1½ g. and INH 600 mg. daily was instituted. This therapy had no effect whatever on the progress of the disease and the patient died on May 18, 1960.

At autopsy he was found to have miliary tuberculosis. There were two caseous foci, the size of a pea, on the upper right lobe and miliary tuberculosis of the liver with a moderate degree of fatty degeneration and sclerosis. The kidneys showed tuberculous foci at the apex of the Malpighian pyramids and there were small disseminated miliary nodules in the peritoneum.

Discussion

The five cases reported had no previous history of tuberculosis. All the patients were given corticosteroids for other diseases, namely two for articular conditions, one for lymphogranuloma, one for sarcoidosis and one for spondylarthrosis. In all five cases chest roentgenograms taken before the institution of corticosteroid therapy were normal. In none were tuberculostatic drugs added to the corticosteroids. The spread of tuberculosis during corticosteroid treatment has been reported by several authors.

Karlson and Gainer (1951) suggest that this spread is due to the fact that the drugs prevent the formation of connective tissue round tuberculous foci. The experimental researches of Spain and Molomut (1950) on guinea pigs showed that tuberculous lesions in these animals are more severe following treatment

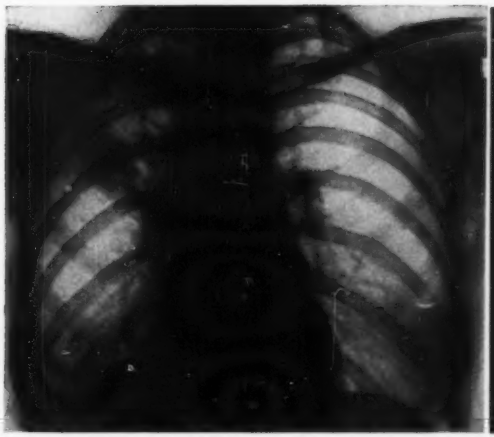

FIG. 1.—Case 1. After six months corticosteroids-therapy. Pulmonary tuberculosis with cavitation of the right lung.

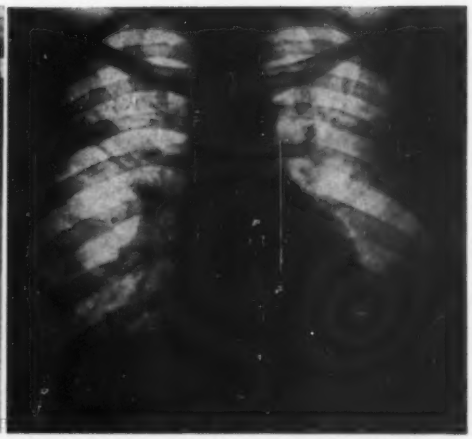

FIG. 2.—Case 2. After eleven months corticosteroids-therapy. Bilateral cavitary pulmonary tuberculosis.

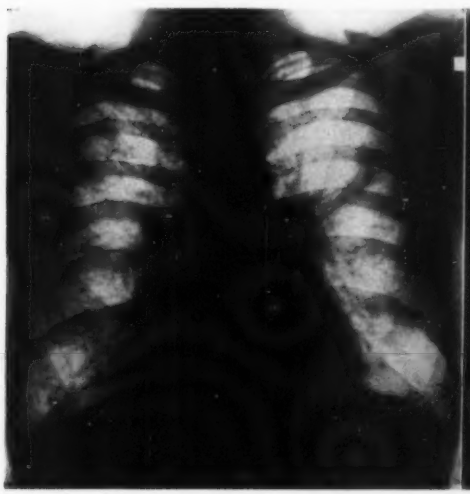

FIG. 3.—Chest roentgenogram of case 3, before corticosteroids-treatment. Bilateral enlargement of the hilar nodes with juxta-hilar infiltration of the left lung and disseminated foci bilaterally-sarcoidosis.

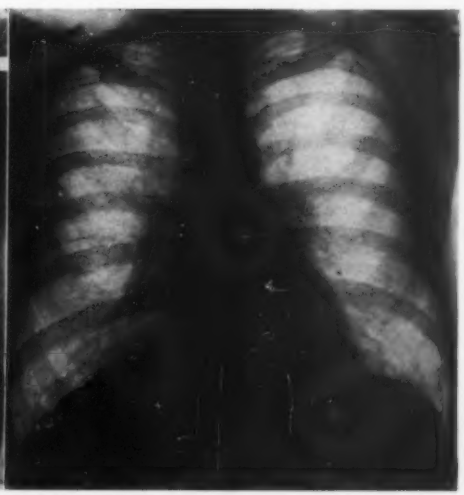

FIG. 4.—Case 3. Two months after corticosteroids-treatment. Complete clearing of the parenchymal lesions, together with a marked regression of the hilar nodes.

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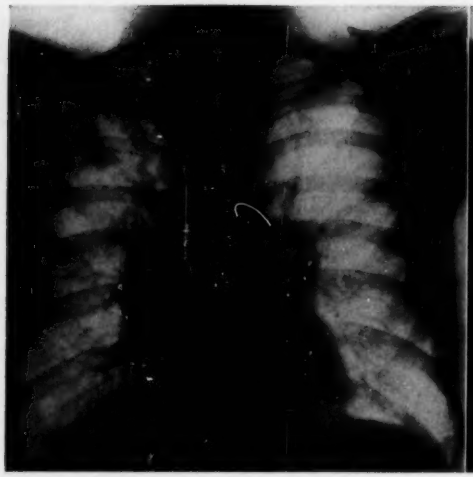

FIG. 5.—Case 3. Four months after corticosteroids-therapy a subclavicular tuberculous infiltrate was revealed.

FIG. 6.—Case 4. After thirty days intermittent corticosteroids-therapy. Right side exudative pleurisy, and disseminated broncho-pneumonic foci bilaterally.

FIG. 7.—Case 5. After one month corticosteroids-therapy. Densemiliary spread bilaterally.

with streptomycin and cortisone than after streptomycin alone. Hart and Rees (1950) believe that the tendency to dissemination following the administration of cortisone cannot be attributed exclusively to deficiency in the formation of fibrous tissue. Michael *et al.* (1950) found that the natural resistance to tuberculosis in mice was reduced with the exhibition of corticosteroids. They believe that this is due to repression of the inflammatory reaction.

Opposing the view that cortisone has an unfavourable effect on tuberculous infection, Lurie *et al.* (1951) believe that the drug can convert the hypersensitivity of a rabbit towards tuberculosis into natural resistance. Mackinnon (1959) believes that the development or spread of tuberculosis in humans following corticosteroid therapy rarely occurs and that when this does happen such forms of tuberculosis respond well to tuberculostatic treatment. Kleinschmidt and Johnston and Hill and Kirshbaum reported cases in which dissemination following cortisone treatment was the cause of death and in one of our cases there was a generalised miliary dissemination.

Hill and Kirshbaum believe that dissemination in man is due to the inhibitory action of cortisone on the formation of connective tissue, a view shared also by Carlson and Gainer (1951), Spain and Molomut (1950) and Davidson *et al.* (1953). The speedy fatal course in our case No. 5, in spite of intensive tuberculostatic treatment, corroborates the views of Hart and Rees (1950) and Solotorovsky *et al.* (1951) that cortisone has an unfavourable influence on the defence of the organism against tuberculosis.

In two of our cases corticosteroids were given in order to control collagen diseases, namely disseminated lupus erythematosus and nodular periarteritis. In both tuberculosis occurred in the lungs. In the international literature seven cases of lupus erythematosis have been reported which were complicated by tuberculosis following steroid therapy (Mackinnon, 1959). In six of these tuberculosis took the form of miliary spread.

In one of our cases the disease for which corticosteroid treatment was instituted was sarcoidosis. Although the relationship between sarcoidosis and tuberculosis is not clearly defined, the corticosteroids are widely used in the treatment of the former. Six cases of sarcoidosis complicated by tuberculosis following corticosteroid treatment have been reported (Lovelock and Stone, 1953; Small, 1951; and Mackinnon, 1959). In our case the diagnosis of sarcoidosis was made because of the bilateral hilar adenitis, the negative Mantoux reaction and the lack of response to tuberculostatic drugs. Prednisolone therapy had a favourable effect on the pulmonary lesions, but three months after the institution of therapy chest roentgenograms revealed infiltration the tuberculous nature of which was proved by the positive tuberculin reaction and the patient's complete response to tuberculostatic drugs.

Conclusions

In view of the relatively frequent tuberculous complications following treatment with corticosteroids the advisability of combining this therapy with tuberculostatic drugs, even if the patient is free from tuberculosis, becomes more and more apparent. In patients in poor physical condition, or with

roentgenographic abnormalities indicating a past tuberculous infection, or with a normal chest roentgenogram but a past history of recently arrested tuberculosis, this combined treatment is necessary. In other cases corticosteroid therapy must be accompanied by frequent roentgenographic control.

Summary

Four cases of pulmonary tuberculosis are reported and one case of generalised miliary dissemination. In each tuberculosis occurred following treatment with corticosteroids for some other complaint. The roentgenographic control previous to the treatment was negative for tuberculosis. In our cases the time elapse between the institution of corticosteroids treatment and the development of tuberculosis varied between one month and a year.

In every case but one (which terminated in generalised miliary dissemination) the tuberculous lesions responded favourably to tuberculostatic treatment. The cortisone treatment was continued in two cases even after the development of tuberculosis, in association with tuberculostatic drugs.

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FIG. 1.—A photograph showing the extent of the swelling from behind.

FIG. 2.—A photograph showing the swelling in the left side of the neck.

To face p. 104

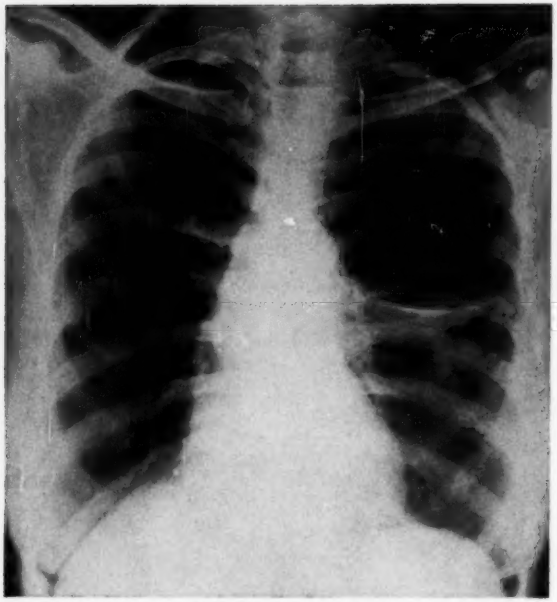

FIG. 3.—A radiograph showing the extent of the emphysematous cyst in the lungs, and its outline in the neck.

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Rare and Interesting Cases

GIANT PULMONARY CYST PRESENTING AS SWELLINGS ON THE ROOT OF NECK AND UPPER PART OF BACK

By A. F. Tuboku-Metzger

Connaught Hospital, Ministry of Health, Sierra Leone, West Africa

Case Report

In 1958 an African woman aged about 60 complained of two swellings on the left side of her neck extending to her back. These were in continuity with another swelling on the left in the upper part of her back. These swellings, she said, increased in size with coughing. They had appeared three months previously, and had grown slowly and were painless. She also gave a history of cough and mucoid sputum.

On examination, the swellings were soft and had the feel of air cushions. There were two large ones in communication with each other (Figs. 1 and 2). One extended from the left clavicle upwards along the left lateral aspect of the neck and posteriorly to the lower four cervical spinal processes. The other, which was larger, occupied most of the area over the trapezius muscle on the same side, meeting the former swelling at the level of the seventh cervical vertebra. On coughing they ballooned to double their original size, deflation was slower and was accompanied by a loud hissing sound. The only positive physical sign in the chest was a diminution of breath sounds over the whole of her left chest and over the right upper zone. The X-ray showed the outline of the air space outside the thorax and what appeared to be a cyst in the upper parts of the right and left lungs (Fig. 3).

A large bore needle was inserted into the base of the larger swelling on the back of her neck and all the air from both cysts was aspirated. The first subsequent cough brought a partial refill and two hours later they had returned to their original size. It was found on further aspiration that pressure behind the lateral end of the left clavicle prevented the external swellings from coming up on coughing. A pad of gauze was applied firmly over that area. Although the swellings recurred they were much reduced. On each occasion when the swellings were aspirated they became less and less. The last tapping was 25 days after the first one and when last seen after a further 2 weeks the swellings had not recurred. Unfortunately, she did not report again.

Comment

This case is reported because of its unusual interest. So far I have not been able to trace in the literature any reports of giant cysts of this size extending into the subcutaneous tissues. A peculiar feature was that the patient walked over three miles to the local dispensary, which was evidence that she was not incapacitated.

I am grateful to Dr. H.M. S. Boardman, O.B.E., Chief Medical Officer, Ministry of Health, Sierra Leone, for permission to publish this case; and to Mr. Alan Curd, of the Photographic Department of the Institute of Diseases of the Chest, Brompton Hospital, for the photograph of the chest X-ray.

Brit. J. Dis. Chest (1961) **55**, 106.

REVIEWS OF BOOKS

The Protection of the Nurse against Tuberculosis. By F. A. H. Simmonds, M.A., D.P.H. London: The Chest and Heart Association. Second Edition. 12s. 6d.

The title of this small book does less than justice to its contents and its purpose. In an admirably clear and concise manner it describes not only the essential measures that should be practised to prevent tuberculosis amongst nurses and other hospital workers, but also those measures designed to protect their general health and welfare. Dr. Simmonds is to be congratulated for compressing in such small compass the needs of hospital staff and the duties of those responsible for providing them. The first chapter deals briefly and simply with tuberculous infection and disease, and, for the lay reader, this should provide a clear understanding of the principles involved in the prevention of tuberculosis. Subsequent sections deal with the selection and medical supervision of staff, tuberculin testing, B.C.G. vaccination, and the environmental requirements of nursing staff. There is a particularly good chapter on the control of sources of infection, and appendices on the National Insurance (Industrial Injuries) Act 1946 and Tuberculosis in Medical Laboratory Workers.

For the nurse and all those who come into close contact with the patient this book is an excellent primer underlining the principles of hygiene. For the medical superintendent, matron, and the lay administrator responsible for the welfare of hospital staff, this is an essential handbook because it advocates those principles which should be standard practice in all hospitals in this country today.

Maxwell Caplin.

Industrial Pulmonary Diseases. A Symposium held at the Postgraduate Medical School of London, 18-20 September, 1957 and 25-27 March, 1958. Editors: E. J. King, Ph.D., D.Sc., F.R.I.C., and C. M. Fletcher, C.B.E., M.D.(Cantab.), F.R.C.P. London: J. and A. Churchill Ltd. 32s.

This comparatively small book is a collection of papers by well-known authorities on the various aspects of pneumoconiosis particularly as seen in Great Britain. The field is well covered and in spite of the many authors the subject matter is co-ordinated into a composite whole. In addition to the purely clinical aspects of the problem there are informative chapters on the physics of dust deposition in the lungs, the value of simple pulmonary function tests in field surveys, the relationship between chronic bronchitis and industry, and occupational lung cancer. Coal-workers' pneumoconiosis, as the most prevalent dust disease of the lungs, rightly receives the most detailed discussion, but more recently recognised occupational hazards are also considered and in this respect the account of stannosis is outstanding. Each chapter concludes with a list of references, the illustrations are clear, and apart from a few spelling errors the book is well produced. It provides an up-to-date and readable account of industrial lung disease in a remarkably small space and is recommended to all interested in the subject.

F. H. Scadding.

Missbildungen des Menschlichen Herzens. By H BARTHEL. Stuttgart: Georg Thieme Verlag. Pp. 237 with 215 illustrations, many of these are coloured. D.M.188.

This not only beautifully illustrated but also very original book deals with the congenital defects of the heart.

In the first part of the work the author demonstrates most ingeniously with the help of models how the effect of torsion and the various strains and stresses on the primitive tubular heart result in endocardial cushions and septa, the latter dividing the two parallel but intertwining blood streams. This experimental approach is unique and throws an entirely new light on this difficult subject.

The second half of the book deals with most of the congenital defects and how they arise. The reading is not easy and demands a very good knowledge of German. The only and minor criticism is that the labelling of the anterior auriculo-ventricular endocardial cushion and the corresponding septal spur in Fig. 83b is wrong and should read O and B-O respectively.

This book is a real contribution to the understanding of the complicated processes which take place in the evolution of the heart and can be strongly recommended to all cardiologists and thoracic surgeons.

H. C. NOHL.

Pages in the History of Chest Surgery. R. NISSEN and R. H. L. WILSON. Oxford: Blackwell Scientific Publications. Illinois: Charles C Thomas. Pp. 166. 60s.

This monograph is a brief survey of the history of thoracic surgery, covering the field from Epaminondas to Lillehei, yet easily read in an hour. The description of scientific advances and individuals is necessarily sketchy and incomplete and the need for inclusion of so many names makes for a staccato style, but the essence of the rapid advance of thoracic surgery is well brought out.

The book will be of particular value to the younger surgeon who has been trained in an era of complete freedom of access to lungs, heart and œsophagus, as a timely reminder of the difficulties of the very recent past. Separate consideration is given to conquest of the problems of an open pneumothorax, thoracotomy, anæsthesia, pulmonary resection, tuberculosis and cardiac and œsophageal surgery, which is a clear and logical sequence.

The title of the book is literal. Many photographed pages of classical articles are reproduced, which would seem of relatively minor interest to most readers and which detract from the general conciseness. Nevertheless, this monograph achieves its purpose of giving a quick, yet comprehensive, review of the development of thoracic surgery from its beginnings.

M. V. BRAIMBRIDGE.

Brit. J. Dis. Chest (1961) **55**, 108.

BOOKS RECEIVED

Pneumoconiosis—Modern Trends. Reports of meetings held by the Chest and Heart Association in Birmingham 1959 and Glasgow 1960. London: The Chest and Heart Association. Pp. 144. 18s. 6d.

Fundamentals and Possibilities in Anti-Tuberculosis Vaccination. By R. Prigge and G. Heymann. Translated by H. Chandler Elliott. Toronto University Press. London: Oxford University Press. Pp. 108. 40s.

THE ECONOMICS OF SIDE EFFECTS

In tuberculosis therapy, use of the usual PAS compounds—the free acid or its sodium salt—very frequently leads to side effects or unwelcome reactions that jeopardize the overall aim of therapy . . . the patient's rapid return to normal living. Of considerable and often overlooked importance—particularly to the TB hospital and its staff—is the effect that such undesirable patient reactions to PAS administration have on the total cost of treatment:

UNDESIRABLE REACTIONS (PASA & NaPAS)	ECONOMIC RAMIFICATION
Anorexia, nausea, vomiting (present in approximately half of patients)[1]	1. *Cost of prepared but untouched or wasted meals.* 2. *Extra physician or nursing time to cope with intolerance problem.* 3. *Patient resistance leading to wastage of medication.*
Toxicity, sensitization or complete intolerance	1. *More prolonged hospital stay.* 2. *Overall cost of special care by physician, nurse and pharmacist—desensitization, dosage adjustment, etc.*
Patient resistance to PAS form and dosage regimen	1. *Cost of medication thrown away by the patient.* 2. *More prolonged hospitalization resulting from inadequate dosage.*

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Although PASKALIUM is more expensive initially than the lowest cost form of PAS it should prove vastly more economical when all factors of anti-tuberculosis therapy are considered.

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Brit. med. J. (1960), 2, 446.
Brit. med. J. (1960), 2, 596.

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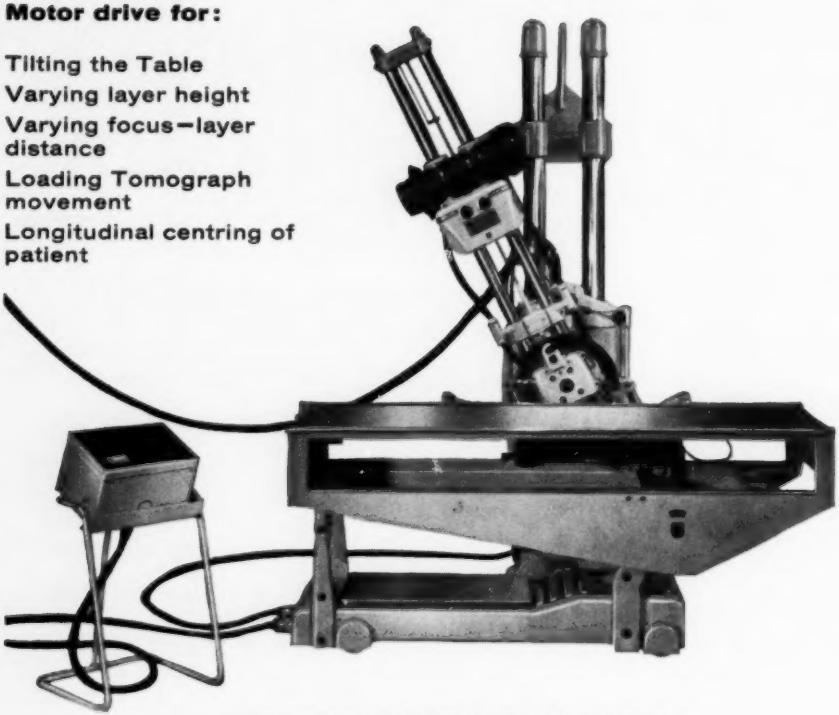

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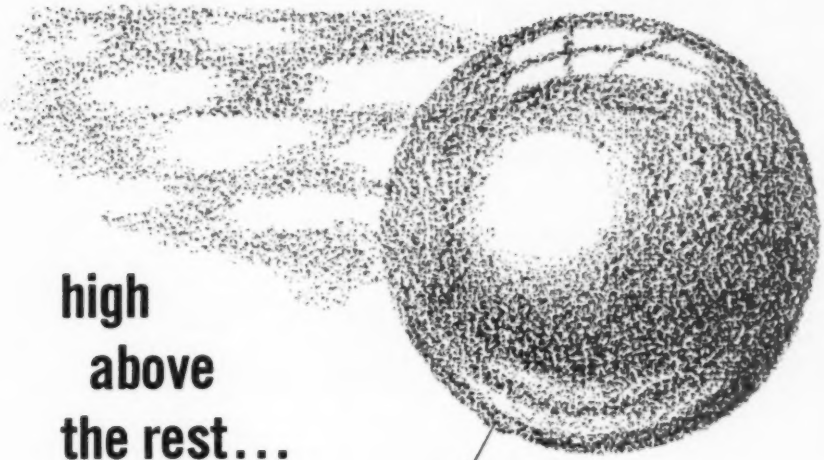

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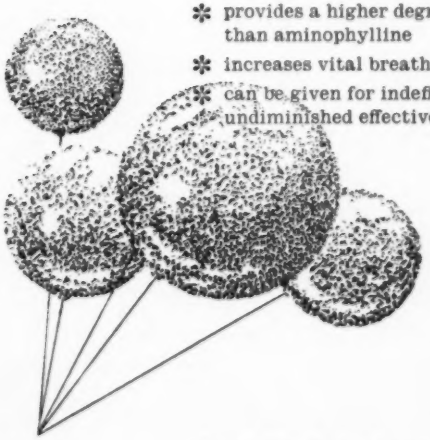

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